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A Further Investigation of Syntheses of the Alkylketodihydroquinazolines.

BY

WILLIAM FLOWERS HAND, M.S.

A DISSERTATION

SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN THE FACULTY OF PURE SCIENCE OF COLUMBIA UNIVERSITY.

NEW YORK CITY.
1903.

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I desire to express my deep appreciation of his valuable assistance throughout the course of the work. Whatever merit it may possess is due to his kindly interest and careful direction.

W. F. H.

Organic Laboratory,
Havemeyer Hall, Columbia University,
New York City.

September, 1903.

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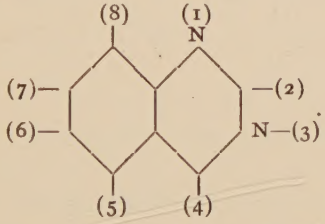
A FURTHER INVESTIGATION OF SYNTHESES OF THE ALKYLKETODIHYDROQUINAZOLINES.

Part I.

The quinazolines or benzometadiazines, benzopyrimidines, or phenmiazines are metameric with the cinnolines, the phthalazines, and with the quinoxalines, though, until recently, the simplest member of this group, the free quinazoline itself, $C_6H_4\begin{cases} N=CH \\ | \\ CH=N \end{cases}$, was not known to exist. Various derivatives, however, have been somewhat carefully studied, and quite a number can be found described in the literature of the subject.

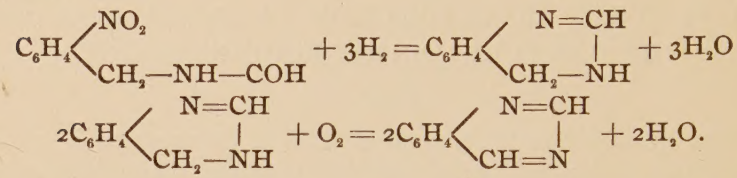
This research deals: First, with those derivatives of the parent body containing oxygen; second, those containing sulphur; and third, those containing bromine and oxygen and bromine and sulphur. The positions of the substituting atoms or groups will be indicated by the use of the following method of numbering the molecule, first suggested by Paal and Busch[1] and adopted in the later reports of the results obtained in this laboratory:



The free dihydroquinazoline, $C_6H_4\begin{cases} N=CH \\ | \\ CH_2—NH \end{cases}$, was prepared by Gabriel and Jansen[2] by reducing orthonitrobenzylformamide with tin and hydrochloric acid, and, by a slight modification of this method, Gabriel[3] was able to obtain excellent yields of the compound. The dihydroquinazoline thus produced was easily

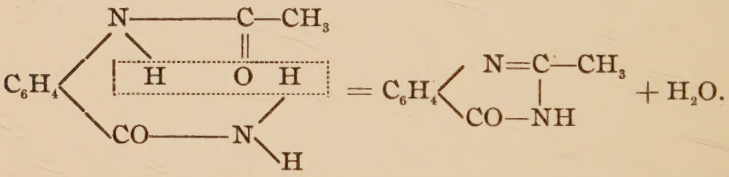
[1] Ber. d. chem. Ges., **22**, 2684.
[2] Ber. d. chem. Ges., **23**, 2813 and **24**, 3097.
[3] Ber. d. chem. Ges., **36**, 800.

converted into the quinazoline by oxidation with potassium ferricyanide:

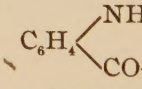


The first quinazoline derivative was prepared by Griess[1] in 1869 by the action of cyanogen upon an alcoholic solution of anthranilic acid. This compound was an ethoxyketodihydroquinazoline which gave a diketotetrahydroquinazoline on boiling with hydrochloric acid.

The 4-ketodihydroquinazoline and some of its alkyl derivatives were first reported by Weddige[2] who prepared the compounds by simply heating above their melting-points the acyl derivatives of orthoaminobenzamide, the effect of the heat being the elimination of water and the completion of the ring structure. It will be shown later that the 2-methyl-4-ketodihydroquinazoline results by a lactam condensation of acetylorthoaminobenzamide:



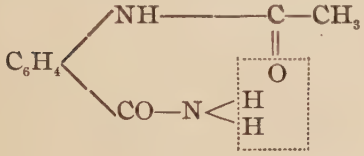
Formylorthoaminobenzamide condenses in a similar way, giving the quinazoline.

In the same year Griess,[3] by the dry distillation of carboxylcyanamidobenzoyl obtained a body melting at 214° and called by him carbimidoaminobenzoyl,  . However, Knape,[4] several years later, repeated the work carried out by Griess and obtained a compound melting at 211°-212°. This substance

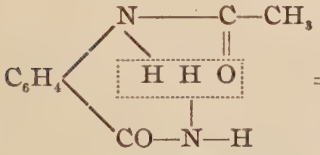
[1] Ber. d. chem. Ges., **2**, 415.
[2] J. prakt. Chem. (2), **31**, 124.
[3] Ber. d. chem. Ges., **18**, 2419.
[4] J. prakt. Chem. (2), **43**, 214.

agreed in melting-point and properties with the 4-ketodihydroquinazoline already prepared by Weddige, and Knape, therefore, concluded that the formula advanced by Griess was incorrect, the body being a true quinazoline.

Later Weddige[1] resumed his work upon the quinazolines and investigated thoroughly the mechanism of the condensations of acylanthranilamides. Taking the case of the acetyl derivative as an illustration, it can be seen at once that the compound may lose the elements of water in one of two ways as shown below, the one being a lactime and the other a lactam condensation:



$= C_6H_4 \begin{cases} NH—C—CH_3 \\ \quad\quad \| \\ CO—N \end{cases} + H_2O$ or



$= C_6H_4 \begin{cases} N=C—CH_3 \\ \quad\quad | \\ CO—NH \end{cases} + H_2O.$

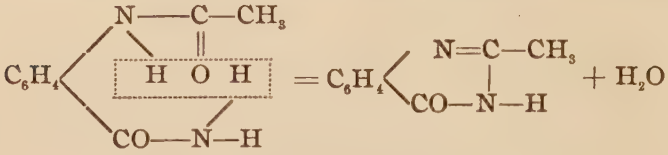
To throw some light on the individual hydrogen atoms concerned in the elimination of water from these bodies, Weddige prepared the acetyl derivative of orthoaminobenzmethylamide,

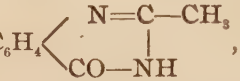
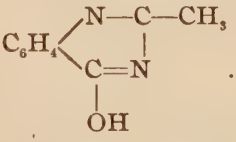
$C_6H_4 \begin{cases} NH—CO—CH_3 \\ CO—NH—CH_3 \end{cases}$ and of methylorthoaminobenzamide,

$C_6H_4 \begin{cases} N < \begin{matrix} CH_3 \\ CO—CH_3 \end{matrix} \\ CO—NH_2 \end{cases}$. Upon condensation, the former of these compounds gave a body, melting at 108°-109°, identical in all respects with the methyl ether of 2-methyl-4-ketodihydroquinazoline, called by Weddige the methyl ether of anhydroacetylorthoaminobenzamide. This ether was prepared by the action of methyl iodide on the sodium salt of the methyl quinazoline. By condensing the methylorthoaminobenzamide, Weddige obtained a compound melting at 199° and, of course, entirely different in

[1] J. prakt. Chem. (2), 43, 214.

properties from the bodies mentioned above. The condensation of the acylamide must have taken place, therefore, as follows:



giving a double bond at 2 instead of at 3, as in the case of a lactam condensation. No preference was indicated for either the keto formula,  , or the corresponding tautomeric enol form,  .

Weddige[1] succeeded also in preparing the 2-methyl-4-ketodihydroquinazoline by heating the ethyl ester of acetylanthranilic acid to 150°-160° with alcoholic ammonia, alcohol and water splitting out on forming the ring. The synthesis would seem to confirm the conclusion already reached in regard to the structure of the quinazolines.

The work of Körner[2] was very similar to that of Weddige, and resulted in the same general conclusions in regard to the course of these condensations. The methyl ethers of 2-phenyl-4-ketodihydroquinazoline prepared by Körner from benzoylorthoaminobenzmethylamide and also by the action of methyl iodide on the sodium salt of the quinazoline were found to be identical, thus supporting the conclusion drawn from previous work with the alkyl derivatives.

It was shown by Paal and Busch[3] that the 4-ketodihydroquinazolines result also by the oxidation of the derivatives of the tetrahydro compounds by the use of alkaline potassium perman-

[1] Loc. cit.
[2] J. prakt. Chem. (2), **36**, 155.
[3] Ber. d. chem. Ges., **22**, 2690.

ganate solution. Paal and Krecke[1] investigated carefully the action of alkaline permanganate on the phenyl ether of 2-methyltetrahydroquinazoline, and found that the first step in the oxidation resulted in the formation of a ketoquinazoline, the methyl group being the next point of attack. The intermediate product was the carboxylic acid, $C_6H_4\begin{cases} N=C-COOH \\ CO-NC_6H_5 \end{cases}$, and this easily lost carbon dioxide.

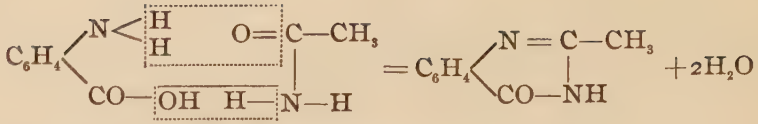
Bischler and Burkart[2] proposed another synthesis in the quinazolon group. They prepared the 4-ketodihydroquinazoline by the action of heat on the ammonium salt of formylanthranilic acid. In this case the heat evidently caused the formation of the formylamide which then condensed to the quinazolone, as has been pointed out in the preceding paragraphs.

Quinazolines were also obtained by Bischler and Lang[3] by the action of alcoholic ammonia on the acyl derivatives of orthoaminobenzophenone, and they showed also that these compounds could be converted readily into the corresponding keto bodies by oxidation with an acetic acid solution of chromic acid. By using this method, the authors prepared the 4-ketodihydroquinazoline and quite a number of its derivatives.

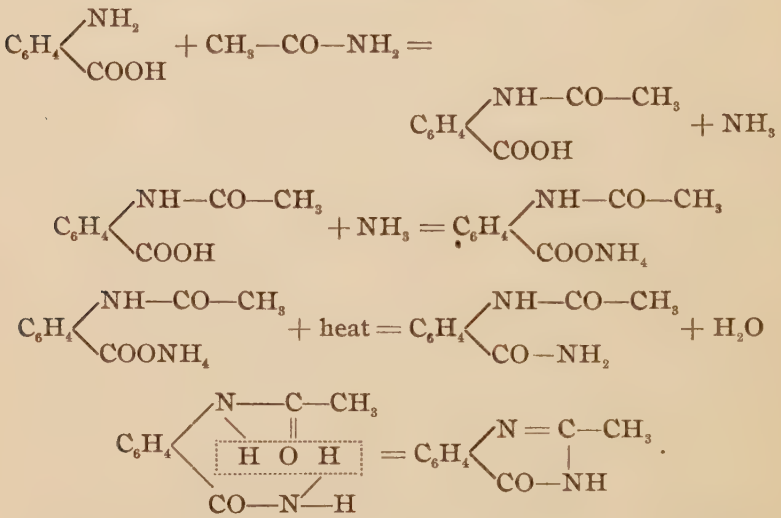
It was pointed out by Niementowski[4] that the quinazolines could be prepared by heating anthranilic acid and fatty acid amides in sealed tubes, the yield of the pure condensation product decreasing with the increase in molecular weight of the fatty acid amide employed. In the case of acetamide, however, Niementowski reported a larger yield than could be secured by Bogert and Gotthelf[5] using the same method.

In the formation of quinazolones from anthranilic acid and amides, it can be seen that the reaction may take the course as given below:

[1] Ber. d. chem. Ges., **24**, 3049.
[2] Ber. d. chem. Ges., **26**, 1349.
[3] Ber. d. chem. Ges., **28**, 279.
[4] J. prakt. Chem. (2), **51**, 564–572.
[5] J. Am. Chem. Soc., **22**, 531.

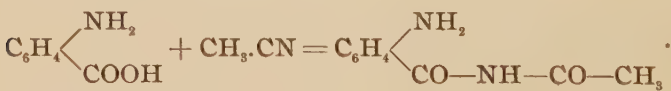


or, as suggested by Bogert and Gotthelf, as follows:

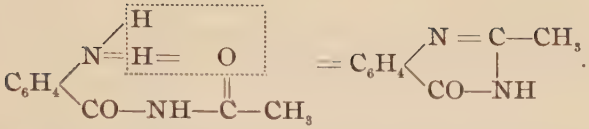


The last named authors think the explanation of Niementowski's synthesis, as outlined in the above reactions, quite possible, as it is known that acetamide and aniline yield acetanilide when heated together, and also in view of the fact that it is the general tendency of higher amines and acetamide to give the amide of the higher acid.

Bogert and Gotthelf[1] in 1900 made a preliminary announcement of an entirely new synthesis of the quinazolines, reporting the preparation of 2-methyl-4-ketodihydroquinazoline by heating anthranilic acid and acetonitrile in sealed tubes. The following explanation of this synthesis was advanced:

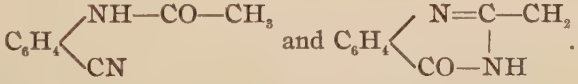


[1] J. Am. Chem. Soc., **22**, 129.



The possibility of the condensation taking place in such a way as to give a double bond at 2 is not excluded, but it has been shown by their later work that the reaction does not take that course, the quinazolines obtained by this method being entirely identical with those described by Weddige who proved that his compounds could not have a double bond at 2.

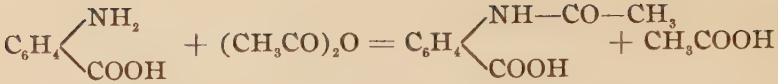
In a later contribution Bogert and Gotthelf[1] discuss their synthesis somewhat in detail. The production of a secondary amide as an intermediate product seemed quite probable. However, it has been shown by Colby and Dodge[2] that aromatic monobasic acid and aliphatic nitriles may give aromatic nitriles and fatty acids when heated together. If the reaction between anthranilic acid and acetonitrile should take place in this way, anthranilic-nitrile and acetic acid would result; the acetic acid would then give the acetylanthranilicnitrile, a compound metameric with the 2-methyl-4-ketodihydroquinazoline. This is seen at once by comparing the formulas,

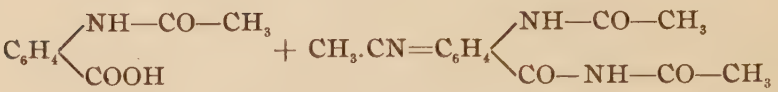


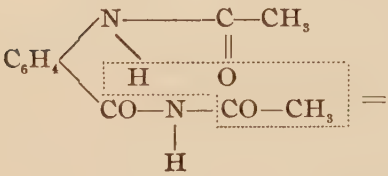
It will be shown, however, in another part of this paper that the rearrangement of the one body into the other does not take place, at least not with the lower acyl derivatives of anthranilic-nitrile.

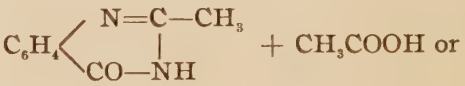
In these syntheses the addition of acetic anhydride to the tube generally increased the yield of the condensation product, probably acting to maintain anhydrous conditions within the tube. Assuming the secondary amide to be the intermediate product, the addition of acetic anhydride will not change the nature of the condensation, as in this case acetic acid, and not water, will be split out on completing the ring:

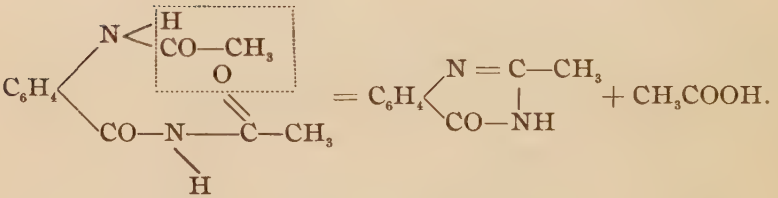
[1] J. Am. Chem. Soc., **22**, 524.
[2] Am. Chem. J., **13**, 1.







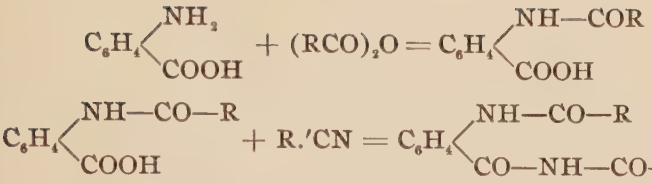




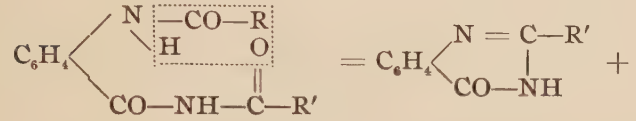
It was shown that acetic anhydride does not react with the quinazolones, and consequently an excess of it in the tube could do no harm in acylating the condensation product.

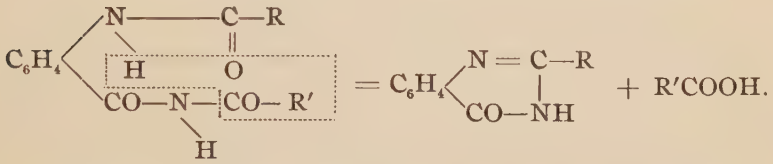
A further careful study of this synthesis of these bodies by this method was made by Gotthelf[1] working in this laboratory. In this investigation, various nitriles were heated with anthranilic acid alone, and also with anthranilic acid and higher and lower acid anhydrides. It was found that when a nitrile was used with a higher anhydride, the anhydride determined the quinazolone produced, for it can be seen that when different anhydrides and acids are employed two distinct quinazolines may result, depending on the fatty acid split out on condensation.

[1] J. Am. Chem. Soc., **23**, 611.



Now, on forming the ring structure, R'COOH or RCOOH may split off.





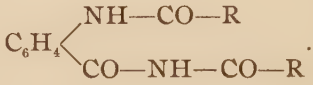
Nitriles and lower acid anhydrides gave mixtures, while the use of both higher and lower fatty acids resulted in mixtures, or the quinazolone obtained depended only on the nature of the nitrile.

It will be seen, therefore, that quite a number of methods of preparing quinazoline bodies have been proposed from time to time, but those worked out by Weddige and by Bogert and Gotthelf seem to be the most direct and convenient. The reactions involved in both processes have been studied with care. The discovery of the reaction between anthranilic acid and nitriles at once opened up quite a broad field for research, inasmuch as the method has been found to be so generally applicable, and so conveniently applied. The work which is outlined in this dissertation was undertaken with the view of making a further study of certain reactions and syntheses which grew out of, or which are based primarily upon, the work already reported from this laboratory.

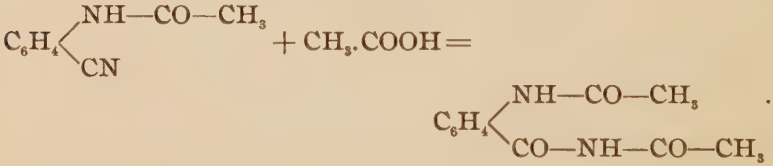
The Synthesis of Alkylketodihydroquinazolines from Anthranilic-nitrile.

In the preparation of alkylketodihydroquinazolines from anthra-

nilic acid and aliphatic nitriles as already described in the foregoing paragraphs, attention has been directed to the hypothetical secondary amide thought to be the momentary intermediate product in the synthesis. This body possesses the following structure:



It can be seen upon examination that the group CO—NH—CO of the above body, being symmetrical, should be formed equally as well by transposing the relative positions of the condensing carboxyl and cyanogen groups. It appeared that RCN and R'COOH would give the same product as R'CN and RCOOH; in other words, as the condensation takes place solely between the CN and the COOH, it seemed immaterial which radical carried the CN and which the COOH. Assuming this to be true, acetylanthranilicnitrile and acetic acid should yield the same secondary amide as anthranilic acid and acetonitrile, as follows:



At higher temperatures, then, the condensation would follow the course already outlined and the quinazoline body would result. It seemed probable also that this method would give better yields than when working with anthranilic acid, since it is well known that the acid loses carbon dioxide quite readily, and since Bogert and Gotthelf[1] have shown that, at the temperature necessary to cause the condensation of anthranilic acid and nitriles, part of the acid breaks down giving aniline and carbon dioxide.

As the result of the practical testing of this idea of preparing the quinazolines from anthranilicnitrile and acids or acid anhydrides, the method was found to give very satisfactory results, the compounds obtained being identical in every way with those pre-

[1] Loc. cit.

pared by the foregoing methods. For some reason, however, the yields were not so good as those reported from anthranilic acid, but the process is still a very convenient one, and, in those cases where the orthoamino acid is best obtained by the saponification of its nitrile, it is much more convenient to be able to pass to the quinazolines directly, saving thereby one step in the synthesis.

Anthranilicnitrile.

This research was very much facilitated on account of the fact that the method of preparing anthranilicnitrile rapidly and in good yield had been carefully worked out by Bogert[1] before the study of these syntheses was undertaken. The starting-point was orthonitraniline, and, considering the number of the operations and the length of the processes, the yield and purity of the final product leave little to be desired. The *o*-nitraniline was converted into the *o*-nitrobenzonitrile by the Sandmeyer reaction, and it was found that the nitronitrile could be entirely freed from the precipitated mineral cyanides by crystallizing from boiling carbon tetrachloride in which the latter are entirely insoluble. Friedländer[2] proposed the use of benzene for purifying the crude nitronitrile from mineral matter; but, since the nitronitrile is much more soluble in cold benzene than in cold carbon tetrachloride, the latter solvent is much to be preferred, the amount remaining in the mother-liquors being small. The old process of purification by distillation in a current of superheated steam may, therefore, be abandoned (Pinnow and Müller[3] and Pinnow and Saemann[4]).

The reduction of the pure nitronitrile is very readily accomplished by the use of stannous chloride and hydrochloric acid, the temperature being controlled by carrying out the reduction in an ice-bath and by regulating the addition of the nitro compound. On completing the reduction, the chloride of the aminonitrile is precipitated by the addition of cold hydrochloric acid in excess, as recommended by Friedländer,[5] the tedious removal of the tin by hydrogen sulphide being thereby wholly avoided. The free base

[1] J. Am. Chem. Soc., **24**, 1035.
[2] Monatsh. Chem., **19**, 627 (1898).
[3] Ber. d. chem. Ges., **28**, 149 (1895).
[4] Ibid., **29**, 623 (1896).
[5] Loc. cit.

is easily recovered from the washed chloride by treatment with ice-cold alkali and collecting with ether. In later work, it was found to be much more convenient and more rapid to grind the chloride of the aminonitrile in a large mortar with a slight excess of dilute ammonia water, the ammonium chloride being afterwards completely removed by washing on a large Witt plate or in a Büchner funnel with ice-cold water. The entire process is very satisfactory, and yields amounting to nearly 90 per cent. of that theoretically obtainable from the nitronitrile have been secured. There was no sign of saponification, though this is contrary to the experience of Pinnow and Müller,[1] Pinnow and Saemann,[1] and Friedländer.

A general outline of the process is given below.

Preparation of o-Nitrobenzonitrile, $C_6H_4\begin{cases}NO_2\\CN\end{cases}$.—The following method of preparing this body was found to give the best results:

13.8 grams of finely pulverized *o*-nitraniline are treated with 17.5 cc. of concentrated hydrochloric acid (sp. gr. 1.187) and the mass stirred until the conversion to the chloride is complete. This operation is best carried out in a large porcelain mortar, as in this all lumps may be thoroughly disintegrated and a fine state of division assured. 500 cc. of water are then added all at once and the mixture stirred thoroughly. The chloride will instantly dissociate and the free base separates in fine flocks which diazotize much more rapidly than finely pulverized *o*-nitraniline. The suspended nitraniline is then diazotized by adding a solution of 7 grams of sodium nitrite in 40 cc. of water, stirring constantly with a turbine. No external cooling is necessary during the diazotizing process, as the diazo compound is remarkably stable at ordinary temperatures, no appreciable decomposition occurring even on standing forty-eight hours at laboratory temperature, and cooling only retards the diazotizing and diminishes the yield of the nitronitrile. At least one hour should be consumed in adding the solution of sodium nitrite, and the mass should then be stirred

[1] Loc. cit.

for another hour, when all the orange nitraniline should be changed to the light-colored, flocculent diazo-compound and starch iodide paper should still show the presence of an excess of nitrous acid. If the vessel is now allowed to stand for a short time, any undiazotized *o*-nitraniline will rapidly settle to the bottom, and, by careful decantation, the suspended diazo-body may be poured off from the heavier nitraniline. It will be found, however, that but little nitraniline escapes diazotizing in a carefully conducted preparation, yet it is always advisable to decant at this point, as otherwise it follows that the nitraniline must be separated later.

The diazo-body is then poured very slowly and with constant stirring into a cuprous-potassium cyanide solution prepared from 25 grams of crystallized copper sulphate, 150 cc. of water and 28 grams of 96 per cent. potassium cyanide. In working with large charges, cyanogen is, of course, evolved in large quantity, and the operation should be conducted under a safe hood. The cuprous-potassium cyanide solution should be maintained at about 90° throughout the addition of the diazo compound. It has been found that the yield of nitronitrile depends largely on the care with which this operation is conducted. If the diazo-body is added very slowly and with rapid stirring, the yield will be satisfactory, provided the temperature is kept at 90°-100°, while a too rapid addition of the diazo mixture, or allowing the temperature of the cyanide solution to sink much below 90°, will diminish the yield considerably. When the addition of the diazo solution is completed, the contents of the vessel are at once raised to boiling. It is necessary to boil only a few minutes. The solution is then rapidly filtered through a folded filter in a hot-water funnel. On cooling, the nitronitrile separates from the solution in long, yellow needles carrying a considerable quantity of mineral cyanides. A large amount of the nitronitrile remains in what at first appears to be tar. This tar must be thoroughly extracted until no crystals can be obtained from it, and experience has shown that six or eight extractions with considerable quantities of boiling water are always necessary. These crystals coming from the tar are, as might be expected, almost free from cyanides, and the actual amount of insoluble tar remaining after the extraction, is very small.

The crude crystals of *o*-nitrobenzonitrile thus obtained are washed with cold water and then dried and pulverized. By extracting this dry material with boiling carbon tetrachloride, the nitronitrile is readily dissolved, while the mineral cyanides are left behind absolutely insoluble. From the carbon tetrachloride filtrate, on cooling, the nitronitrile crystallizes almost completely in beautiful, golden-yellow scales which carry any unseparated nitraniline, and the amount of this latter substance present may be roughly estimated by the depth of the color of the crystals and the extent of the orange-colored ring on the filter paper used. A single crystallization of the nitronitrile from moderately dilute acetic acid will remove the nitraniline and the body will separate in nearly colorless crystals, melting at 109° (corr.). By a further crystallization from dilute acetic acid, the melting-point may be raised to 109.5° (corr.), at which point it remains constant.

Twelve grams of the crude nitronitrile should be obtained by operating upon 13.8 grams of *o*-nitraniline, a yield of 87 per cent. of the weight of nitraniline used, and the yield is equally good when working with five to ten times the above charges. The yield of pure crystallized *o*-nitrobenzonitrile (m. p. 109.5°, corr.) should amount to 70 per cent. of the weight of the nitraniline in a carefully conducted preparation. The quantity of mineral cyanides carried down may vary somewhat—of 285 grams of crude nitronitrile obtained in one experiment working with large quantities, 28 grams consisted of mineral matter insoluble in boiling carbon tetrachloride.

The process outlined above is based upon that of Sandmeyer[1] with certain improvements suggested by Pinnow and Müller,[2] and also by Friedländer,[2] together with certain modifications worked out by Bogert. Pinnow and Müller[2] recommend the use of much more concentrated solutions, though their process will be found far less satisfactory than the one given above. So little water is used in their method that the diazo mixture forms a stiff paste which it is very difficult to stir properly, and the yield of crude nitronitrile is smaller and richer in mineral cyanides.

[1] Ber. d. chem. Ges., 18, 1492 (1885).
[2] Loc. cit.

few hours at most. If the chloride of the aminonitrile begins to separate towards the end of the reduction, it can be brought into solution again by the cautious addition of water. When all the nitronitrile has been reduced, a large volume of concentrated, cold hydrochloric acid is added and the vessel is left packed in ice for about eighteen hours. By this treatment nearly all of the aminonitrile will be thrown out as the chloride, and the fine, white, granular crystals can be collected on asbestos and washed with ice-cold concentrated hydrochloric acid to remove the tin. The amount of the chloride remaining in solution is usually very small, and is not sufficient to pay for the expenditure of time and trouble necessary to recover it. Of course, if the reducing solution be too greatly diluted with water, the precipitation with hydrochloric acid will be much less complete, and it may become advisable then to work over the mother-liquor. The yield of aminonitrile from this process may amount to 80 per cent. of that theoretically obtainable from the nitronitrile. A further small quantity may be recovered from the acid mother-liquors. After washing the precipitated chloride and sucking as dry as possible, the free base may be liberated and recovered in the pure state by either of the following methods, the latter being more rapid and convenient:

(1) The chloride is added to a mixture of ice and ether contained in a separatory funnel, and sodium hydroxide solution added with care until an alkaline reaction is shown. The mixture is then well shaken, the ether poured off and the residual aqueous solution extracted with ether three or four times. The ethereal extracts are combined, dried with calcium chloride, the ether distilled off, and the brown, liquid residue placed *in vacuo* over concentrated sulphuric acid, where it soon solidified to a light brown, crystalline cake, melting at 49° (corr.).

(2) To the washed chloride contained in a capacious mortar, an excess of dilute ammonia water is added and the mixture well stirred with the pestle. Small pieces of ice are thrown in to keep the temperature as low as possible, that the loss of nitrile, on account of its slight solubility in cold water, may be kept at a minimum. After washing free of ammonium chloride, the base is dried and dissolved in boiling carbon bisulphide, from which it

separates almost completely on cooling to a few degrees below 0. The yield of pure aminonitrile by this process is usually about 85 per cent. of the theoretical. In the preparation of a comparatively large quantity of the compound, the formation of nitro or aminobenzamide has not been observed. The crystals which sometimes separate during the reduction are only those of the chloride of the base. The free base obtained always dissolved instantly in cold benzene when tested, while the *o*-nitro and *o*-aminobenzamides are soluble in benzene with difficulty.

Properties of Orthoaminobenzonitrile.—The melting-point of the crude aminonitrile is 49° (corr.), though, by recrystallization from carbon bisulphide, this can be raised usually to 49.5° (corr.). Friedländer[1] gives the melting-point as 50°-51°.

The pure product crystallizes in colorless, glassy, monoclinic prisms. By the slow cooling of a carbon bisulphide solution, superb prisms of light yellow cast, fully two inches long and a quarter of an inch thick, have been obtained. It is easily soluble in chloroform, methyl alcohol, ethyl alcohol, ethyl nitrate, absolute ether, acetone, ethyl acetate, carbon bisulphide, benzene, nitrobenzene, and pyridine; easily soluble in carbon tetrachloride and isoamyl alcohol; moderately soluble in cold oil of turpentine, very easily on boiling; difficultly soluble in cold water, moderately at boiling-point; insoluble in cold concentrated ammonia water, moderately soluble on boiling; insoluble in cold petroleum ether or benzine, slightly soluble on boiling. From boiling water, the substance often separates as an oil which only slowly solidifies on standing for some time. Occasionally, glassy blades may be obtained from water; but, if these are left in solution for a few days, they become white and opaque, and then show a lower melting-point (46°-47°). The carbon bisulphide solution shows an interesting behavior. It is very sensitive to changes of temperature, and from a solution prepared at the ordinary temperature of the laboratory the compound was separated almost completely by cooling to — 12° by ice and concentrated hydrochloric acid. The large crystals formed by spontaneous evaporation of the solution at ordinary temperature may redissolve rapidly and completely by a slight elevation of the temperature of the room.

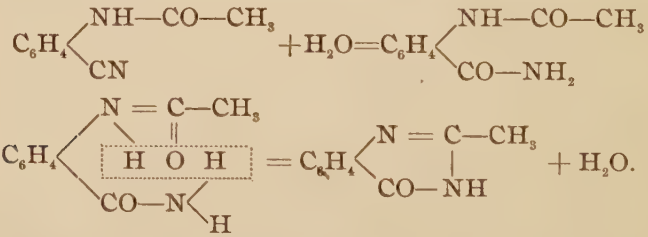
[1] Loc. cit.

The Action of Acids and Acid Anhydrides on Anthranilicnitrile and the Preparation of Acyl Derivatives.

The pure anthranilicnitrile having been obtained in good quantity, some of its acyl derivatives were isolated and further investigated. It is interesting to note that these compounds, like the quinazolines obtained from them later, exhibit a decrease in melting-point with an increase in molecular weight, and the iso-compounds melt at a higher temperature than those possessing a normal structure.

The lower acylanthranilicnitriles can be prepared with great ease by boiling, for some time, with the anhydride of the acid, and they seem to show no tendency whatever to rearrange into the isomeric quinazoline body. To determine if it were possible to cause a rearrangement of the acetyl derivative by heating under pressure in a sealed tube, as in preparing the ketodihydroquinazolines, a quantity was heated for some time above its melting-point in toluene solution, toluene having a boiling-point near that of acetic anhydride and giving approximately the same pressure in the tube. The rearrangement shown below could not be brought about under the conditions of the experiment.

Nevertheless, some of the higher acyl-compounds do show a decided tendency to pass over into the quinazoline structure, probably by the addition and splitting off of the elements of water.



takes place. In one attempt to prepare the *n*-butyryl compound, a body was obtained, which melted quite sharply at 201° (corr.), the melting-point of the quinazoline, $C_6H_4\langle^{N=C-C_3H_7}_{CO-NH}$, being 201°-202° (corr.).

The description of the preparation and properties of the propyl, *n*-butyryl, and isobutyrylanthranilicnitriles, given later, is taken from the work of Bogert.[1] Inasmuch as the tendency toward rearrangement seems to increase with the molecular weight, it is somewhat strange that it was not difficult to obtain a pure isovalerylanthranilicnitrile, whereas, difficulty was found in working with the normal and isobutyryl compounds. In the latter case, however, carbon tetrachloride was used in purifying by recrystallization (see page 30) and it may be that any adaptable anhydrous solvent would have given good results in all cases. In any case, boiling with the anhydride, and afterwards in dilute alcohol, or in water, should not be continued longer than absolutely necessary.

(*1*) *Hydrochloride of o-Aminobenzonitrile.*—To prepare this salt, the nitrile (carefully dried over sulphuric acid) was dissolved in absolute ether and a stream of carefully dried hydrochloric acid passed into the solution. The chloride was thrown out immediately. The perfectly white mass was filtered rapidly, and washed thoroughly with dry ether. It was found that the salt dissociates instantly when placed in water and even gives off hydrochloric acid rapidly in moist air. A quantity dried rapidly was analyzed with the results given below. An exact chlorine content was hardly to be expected, but it was thought, by rapid work, an approximate result would be obtained.

0.2170 gram gave 0.1995 gram AgCl.
1.0000 gram gave 0.9248 gram AgCl.

	Calculated for $C_6H_4\langle^{NH_2.HCl}_{CN}$.	Found.	
		I.	II.
Cl	25.76	22.88	22.07

The above figures illustrate the rapid dissociation of the salt even in the air.

[1] J. Am. Chem. Soc., **24**, 1045.

The chloride, however, dissolves quite readily in absolute alcohol and moderately easy in boiling toluene; slightly soluble in glacial acetic acid (with partial dissociation) and apparently insoluble in chloroform, carbon tetrachloride, benzene, absolute ether, ligroïn, and acetone.

It is to be noted, however, that Pinnow and Müller[1] state that this chloride crystallizes in beautiful tablets which are quite stable, although they admit that the crystals show a tendency to dissociate in aqueous solution, while Pinnow and Saemann[1] even attempted to separate anthranilic nitrile from the corresponding amide by fractional crystallization of their chlorides from water. The experience concerning the stability of the chloride of anthranilicnitrile in aqueous solutions that has been encountered in this work is quite at variance, therefore, with the statements of the above authors. However, in concentrated hydrochloric acid the chloride appears to be quite stable, though this is to be expected.

(2) *Formylanthranilicnitrile,* $C_6H_4\begin{cases}NH—COH\\CN\end{cases}$.—The action of glacial formic acid upon anthranilicnitrile was somewhat confusing. Five cc. of glacial formic acid were poured over 5 grams of the nitrile, causing the latter to dissolve with the evolution of considerable heat. The solution was gently boiled on a sand-bath for two hours and then allowed to cool, when the contents of the flask set to a yellow crystalline cake, a portion of which decomposed at 200° with the evolution of gas. The cake itself is composed of several substances, and there were separated from it white, warty masses which dissolved easily in boiling water; also long, yellow needles apparently insoluble in boiling water and difficultly soluble in boiling alcohol, and a flocculent, yellow substance which dissolved in 95 per cent. alcohol. None of the above substances were secured in sufficient quantity and purity for an accurate analysis. Another quantity of the nitrile and formic acid, heated over a water-bath for several hours, also set to a solid mass on cooling. This yellowish cake

[1] Loc. cit.

was boiled out with absolute alcohol when a portion dissolved, separating from the strong alcoholic solution in yellow flocks. These were insoluble in 20 per cent. potassium hydroxide solution. The residue from the alcohol extraction was boiled out with water, though the water dissolved only a small quantity of the mass and nothing crystalline could be obtained. The solutions from the above extractions often exhibited a striking light blue fluorescence. The white, warty masses mentioned above were evidently the formyl derivative of the aminonitrile, as it will be shown later that the quinazolone was obtained from them.

(3) *Acetylanthranilicnitrile,* $C_6H_4\begin{cases}NH—CO—CH_3\\CN\end{cases}$.—Anthranilicnitrile dissolves quite readily in acetic anhydride with the absorption of considerable heat, though this heat is soon given off again, the temperature rising rapidly. On allowing the mixture to cool slowly, a solid, crystalline cake is formed in the vessel. This cake is melted by gentle warming and boiled on the sand-bath for a few hours. The hot liquid is then poured into twice its volume of boiling water and the whole boiled for a few minutes to decompose the excess of acetic anhydride, and, on cooling, the acetyl derivative separates out in long, white, silky needles melting at 132.5° (corr.). This agrees with the melting-point already found by Pinnow and Saemann.[1] The fusing-point could not be changed by further crystallization from water. By heating for some time above its melting-point, no rearrangement to the isomeric 2-methyl-4-ketodihydroquinazoline was noted.

In the course of other work in this laboratory, it was noticed in the preparation of acetylanthranilicnitrile that, on crystallizing the crude product from water, there was obtained a small amount of a substance crystallizing in perfect, small cubes of a faint yellowish cast, which melted sharply at 91°, but the quantity obtained was too small for analysis. These cubes, however, were not detected in any of these experiments.

Properties of Acetylanthranilicnitrile.—The white needles are very soluble in methyl alcohol, ethyl alcohol, isoamyl alcohol,

[1] Loc. cit.

ethyl nitrate, ether, acetone, ethyl acetate, glacial acetic acid, acetic anhydride, and nitrobenzene; easily in carbon bisulphide, benzene, and oil of turpentine; moderately easily dissolved by carbon tetrachloride, or cold water; easily soluble in water at the boiling-point; insoluble in cold petroleum ether or benzine in the cold, and also difficultly soluble at the boiling-point. Long boiling in aqueous solution tends to prevent the crystallization of the substance, giving a milky solution which slowly deposits a fine floury sediment. It is not readily extracted from its aqueous solutions by ether, and, from petroleum solvents, it crystallizes in pulpy masses of minute needles difficult to filter, and which pack down upon the paper, forming a sort of skin. Good crystals may be obtained from water and also from mixtures of naphtha and chloroform, naphtha and ether, or chloroform and carbon tetrachloride. It can be slowly sublimed at 100° in colorless, transparent needles, and it is also volatile with steam. It will be shown later that it may be converted into the 2-methyl-4-keto-dihydroquinazoline by heating in a sealed tube with glacial acetic acid or with acetic anhydride.

(4) *Propionylanthranilicnitrile*, $C_6H_4\begin{cases}NH—CO—CH_2—CH_3\\CN\end{cases}$.—

The action of propionic anhydride and anthranilicnitrile was studied by Bogert[1], and its preparation and properties are included here to make the series of acyl derivatives complete, as far as the work was taken.

Five grams of the nitrile were mixed with 7 cc. of propionic anhydride, and the nitrile was found to dissolve slowly in the anhydride with the absorption of a considerable quantity of heat; the solution then gradually warmed up again and finally solidified to a crystalline cake on cooling. This mass was boiled gently for several hours, and the product was bone-blacked and crystallized from alcohol. Beautiful, colorless, glassy prisms were thus obtained, melting at 119° (corr.). If the crystals are heated quickly, they melt much lower than this; they liquefy in boiling water and sublime at 100° in long, colorless needles. The crystals are difficultly soluble in boiling water and nearly insoluble in

[1] J. Am. Chem. Soc., **24**, 1045.

cold; readily soluble in alcohol. They dissolve in cold, 5 per cent. aqueous potassium hydroxide solution and are not reprecipitated when this solution is acidified with hydrochloric acid, but an excess of ammonia water precipitates the original substance from the acid solution. The compound is also volatile with steam. A portion was prepared for analysis by drying to constant weight *in vacuo* over sulphuric acid. This gave 16.89 and 16.44 per cent. of nitrogen. Calculated for $C_6H_4\begin{cases}NH—CO—C_2H_5\\CN\end{cases}$, 16.64 per cent.

When heated in a sealed tube with propionic acid, or warmed with an alkaline hydrogen dioxide solution, 2-ethyl-4-ketodihydroquinazoline results.

(5) *Normalbutyrylanthranilicnitrile,*

$$C_6H_4\begin{cases}NH—CO—C_3H_7\\CN\end{cases}.$$

—The normalbutyryl derivative was prepared in pure condition by Bogert,[1] using 5 grams of aminonitrile and 8 cc. of *n*-butyric anhydride. The nitrile dissolves slowly with the absorption of heat, but the mixture does not warm up or appear to change on standing. The solution is boiled for an hour, and the crude product crystallized from dilute alcohol and bone-blacked, giving colorless, glassy needles, or long, flattened prisms. By the repeated crystallization of the crude product, a sharp melting-point of 89°-89.5° (corr.) was obtained. The crystals are difficultly soluble in water, but dissolve easily in alcohol, and volatilize with steam. With 5 per cent. aqueous potassium hydroxide solution, followed by hydrochloric acid and ammonia, this compound behaves like the propionyl derivative.

When heated in a sealed tube, or warmed with alkaline hydrogen dioxide solution, 2-*n*-propyl-4-ketodihydroquinazoline is produced.

(6) *Isobutyrylanthranilicnitrile,* $C_6H_4\begin{cases}NH—CO—CH(CH_3)_2\\CN\end{cases}$.—

[1] Loc. cit.

The *i*-butyric anhydride and anthranilicnitrile were heated together as in a previous preparation of these bodies, and the crude product was crystallized from dilute alcohol until the melting-point remained constant at 111°-111.5° (corr.). This acyl derivative forms long, white, silky needles, which are slowly soluble in cold carbon tetrachloride or benzene, but easily soluble on boiling; difficultly soluble in carbon bisulphide, petroleum ether and gasoline; easily soluble in cold ether and in alcohol. It may be sublimed slowly at 100° and volatilizes with water vapor. A sample dried to constant weight gave the following results upon analysis: Carbon, 70.21 and 70.22; hydrogen, 5.84 and 5.83.

Calculated for $C_6H_4\begin{cases}NH—CO—CH(CH_3)_2\\CN\end{cases}$, carbon, 70.21; hydrogen, 6.38.

When heated in a sealed tube with *i*-butyric anhydride, or warmed with alkaline hydrogen dioxide solution, the product is 2-isopropyl-4-ketodihydroquinazoline.

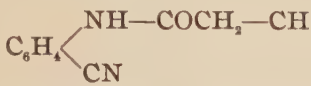
(7) *Isovalerylanthranilicnitrile,*

$$C_6H_4\begin{cases}NH—CO—CH_2—CH(CH_3)_2\\CN\end{cases}.$$

—In treating anthranilicnitrile with *i*-valeric anhydride, the difficulty of obtaining a compound of sharp melting-point was experienced, as in the cases of other higher anhydrides, until carbon tetrachloride was used to purify the crude product. Repeated recrystallizations from dilute alcohol failed entirely to give a compound of a satisfactory melting-point. In earlier efforts to obtain a pure body, various crops of crystals were obtained, which melted as follows: 100°-109°, 106°-108°, 107°-109° and 106°-108°. These were now added together and the entire quantity crystallized from carbon tetrachloride, as mentioned above, when beautiful, fine needles separated which melted at 105.5° to 106.5° (corr.). The crystals are only moderately soluble in the cold tetrachloride, but dissolved very readily on warming; difficultly soluble in water, readily in alcohol. They liquefy in boiling water and volatilize with steam. When heated in a sealed tube

with *i*-valeric anhydride, or warmed with an alkaline hydrogen dioxide solution, the product is 2-isobutyl-4-ketodihydroquinazoline.

A portion of the substance dried to constant weight, gave 14.01 per cent. of nitrogen. Calculated for

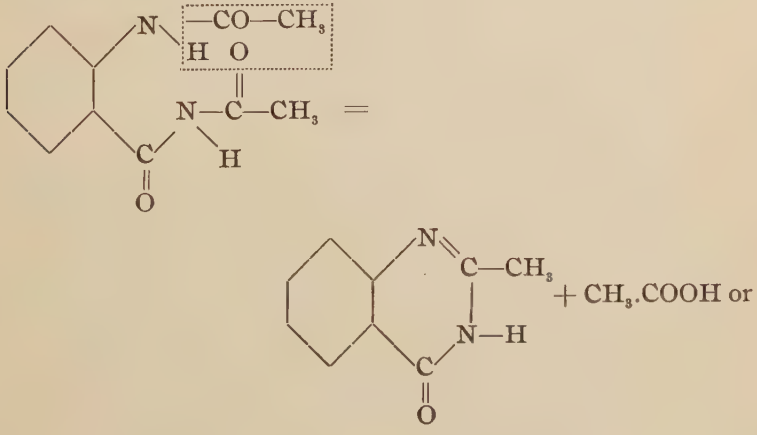


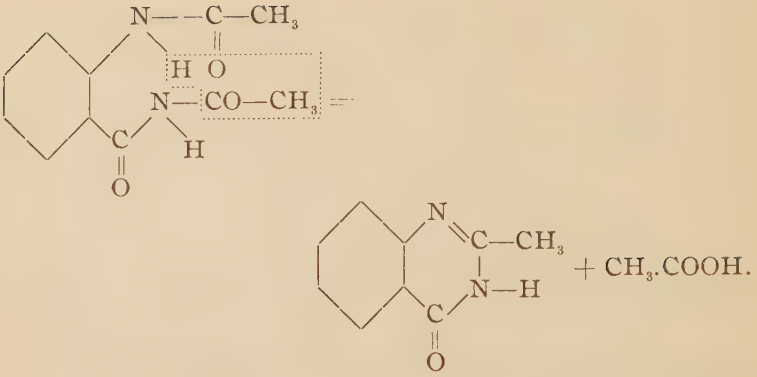
, 13.86 per cent.

The Preparation of 2-Alkyl-4-ketodihydroquinazolines by Heating Anthranilicnitrile in Sealed Tubes with Aliphatic Acids or Their Anhydrides.

The anthranilicnitrile prepared as described was heated in sealed tubes with glacial formic acid, and also with the anhydrides of acetic, propionic, normalbutyric, isobutyric, and isovaleric acids. From the experiments conducted with formic acid on the nitrile, no satisfactory results could be obtained. If the formylanthranilicnitrile is formed at all under the conditions of these syntheses, it decomposes or does not condense in the same manner as the higher acyl compounds. In all other cases tried, the quinazolines were obtained as expected.

By the use of the acid anhydrides the first products of the reaction, are the acylanthranilicnitriles and the free fatty acid which then react at higher temperatures with the production of the quinazolines. In this case the presence of water in the tube is avoided altogether; and, if the temperature be regulated properly, only a small quantity of tar is produced:





(1) *Anthranilicnitrile and Glacial Formic Acid. 4-Ketodihydroquinazoline,* $C_6H_4\begin{cases}N=C-H\\ \quad\quad|\\ CO-NH\end{cases}$.—As already stated, this quinazoline could not be obtained by this method. 2.5 grams of the nitrile were placed in a strong tube with 3 cc. of glacial formic acid and heated at 270°-284° for eight hours. The contents of the tube were completely soluble in 95 per cent. alcohol, and, from the concentrated alcoholic solution, small, ball-like masses separated on the bottom and sides of the beaker. These were collected and dried and were found to soften at about 100°, but liquefied completely at 160°. The quantity was small. Several unsuccessful attempts to prepare the quinazoline in this way were made. Knape[1] gives the melting-point of this body as 211°-212°, while melting-points from 209° to 216° have been also reported.

(2) *Anthranilicnitrile and Acetic Anhydride. 2-Methyl-4-ketodihydroquinazoline,* $C_6H_4\begin{cases}N=C-CH_3\\ \quad\quad|\\ CO=NH\end{cases}$.—This quinazoline was prepared by heating 2.5 grams of nitrile and 3 cc. of acetic anhydride to 274°-282° for ten hours. The tube contained a brown, crystalline product which was removed and bone-blacked in an alcoholic solution. It was found necessary to use two portions of char to whiten the crystals. About 0.7 gram of the pure quinazoline was finally obtained. This melted at 237.5°-238.5°

[1] J. prakt. Chem. (2), **43**, 217.

(corr.). The compound was identical in all respects with that obtained from acetic anhydride, acetonitrile, and anthranilic acid.

From boiling water it separates in short, glassy needles. If desired, the crystalline mass in the tube may be well washed with ether and crystallized from nitrobenzene. The crystals from the nitrobenzene may then be washed with naphtha and petroleum ether, dried and crystallized from water or from very dilute alcohol.

Properties of 2-Methyl-4-ketodihydroquinazoline.—The properties of this compound were fully investigated by Bogert.[1] The crystals are very easily soluble in glacial acetic acid and also in concentrated potassium hydroxide solution; they are soluble with difficulty in petroluem ether, naphtha, carbon tetrachloride, ethyl nitrate, ether, acetic anhydride, carbon bisulphide, benzene, xylene, cymene, and concentrated hydrochloric acid; difficultly soluble in cold water, chloroform, acetone, ethyl acetate, or oil of turpentine, but moderately soluble in the same solvents at the boiling-point. An alcoholic solution of the base, treated with concentrated hydrochloric acid, gives an immediate white precipitate of the hydrochloride. The latter sublimes unchanged and is less soluble in dilute hydrochloric acid than in water. The crystals of the free base and also of the chloride frequently show a faint yellowish green cast.

Some of the carefully purified crystals were dried to constant weight at 135° and analyzed.

I. 0.1814 gram substance gave 29.1 cc. nitrogen at 23° and 748 mm. pressure = 17.78 per cent. nitrogen.

II. 0.2000 gram substance gave 0.4960 gram carbon dioxide and 0.0900 gram water = 67.63 per cent. carbon and 5.00 per cent. hydrogen.

	Calculated for $C_9H_8ON_2$.	Found. I.	Found. II.
Nitrogen	17.50	17.78	....
Carbon	67.50	....	67.63
Hydrogen	5.00	....	5.00

The picrate was prepared and recrystallized from water; it forms yellow prisms which melt at 207.5°-208.5° (corr.).

[1] Loc. cit.

(3) *Anthranilicnitrile and Propionic Anhydride. 2-Ethyl-4-ketodihydroquinazoline,* $C_6H_4\langle^{N=C-C_2H_5}_{CO-NH}$. —2.5 grams of the nitrile and 3 cc. of propionic anhydride were placed in the tube and heated for five hours at 250° and then for three hours at 275°-280°. No pressure was evident on opening, and the contents of the tube were dissolved in boiling alcohol, and the solution thoroughly bone-blacked, filtered hot and concentrated. On cooling, brownish crystals separated out, which melted at 220°-231°. These were evidently a mixture of the propionylanthranilicnitrile and its condensation product, the ethylquinazolone. They were washed with boiling water and again crystallized from dilute alcohol; the brownish crystals separating were found to melt at 220°-232°. As the amount of these crystals was small, further purification was deemed useless, the reaction being evidently incomplete.

A second tube was prepared in the same manner as the first and contained the same charge. On account of the evident incomplete condensation in the previous tube, it was decided to heat this one for a longer period, hoping to complete the reaction. The temperature of the bomb-oven was kept at 270°-280° for six and a half hours, and at 230° for two hours, and, finally, 274°-285° for six hours longer. There was no pressure in the tube when cold, and its crystalline contents were repeatedly crystallized from carbon tetrachloride, yielding a body which was easily soluble in the boiling tetrachloride, but difficultly soluble in the cold. The crystals seemed to be perfectly pure and melted at 232.5°-233.5° (corr.), beginning to soften somewhat at 231°. They were found to be identical in all their properties with the 2-ethyl-4-ketodihydroquinazoline prepared from anthranilic acid, the melting-point of which was 234° (corr.).

The picrate melted at 193°-194°, while that obtained from the quinazoline prepared from anthranilic acid melted a trifle lower (191°-192°).

(4) *Anthranilicnitrile and Normalbutyric Anhydride. 2-Normalpropyl-4-ketodihydroquinazoline,* $C_6H_4\langle^{N=C-C_3H_7}_{CO-NH}$. —The

normalbutyric anhydride and anthranilicnitrile were sealed in the tube in the usual manner, using 2.5 grams of nitrile and 3 cc. of the anhydride. The tube was heated for four hours at 130°-211° and then for seven hours at 210°-212°, and finally for three hours longer at 215° to 255°. The crystalline product was dissolved in boiling alcohol, and the solution bone-blacked, filtered hot and the filtrate was concentrated, when small crystals of the quinazoline separated on standing for some time. These were collected and again recrystallized from dilute alcohol and were found to melt sharply at 200°-200.8° (corr.). The compound is identical with that obtained in the synthesis from anthranilic acid; it may be crystallized from water in small needles.

The picrate was prepared and carefully purified by repeated recrystallization, and was found to melt at 184.5°-185.5° (corr.). Gotthelf[1] gives the melting-point of this picrate as 183°-184° (corr.).

(5) *Anthranilicnitrile and Isobutyric Anhydride. 2-Isopropyl-4-ketodihydroquinazoline,* $C_6H_4\begin{cases} N = C—CH(CH_3)_2 \\ CO—NH \end{cases}$.—2.5 grams of anthranilicnitrile and 3 cc. of the anhydride were placed in the tube and heated for six hours at 224°-229° and then for six and a half hours longer at 275°. The tube was under no pressure after cooling, and the crude crystals were purified in the same manner as outlined in the preceding paragraph for the *n*-propyl compound. The crystals which separated from the alcoholic solution were further recrystallized from dilute alcohol from which solvent it separated in small, colorless needles melting at 231.5°-232° (corr.), agreeing in all their properties with the 2-isopropyl-4-ketodihydroquinazoline obtained from anthranilic acid.

The picrate was found to melt at 208.5°-209.5°, and this melting-point could not be changed by recrystallizing further. Gotthelf[2] reported the picrate of this quinazolone as melting at 213°-214°. This is evidently a mistake, however, as a melting-point determination on his own sample gave 208°-208.5° (corr.). All of these picrates show slight evidences of fusion one or two degrees below the melting-points recorded.

[1] J. Am. Chem. Soc., **23**, 611.
[2] Loc. cit.

(6) *Anthranilicnitrile and Isovaleric Anhydride. 2-Isobutyl-4-ketodihydroquinazoline,* $C_6H_4\begin{cases} N=C-CH_2-CH(CH_3)_2 \\ \quad\quad\quad | \\ CO-NH \end{cases}$.—The tube for the isobutyl compound was prepared as indicated above. 2.5 grams of nitrile and 3 cc. of isovaleric anhydride were used, and the heating continued for six hours at 224°-229° and then for six and a half hours at 275°. No pressure was shown when the cold tube was opened, and the crude crystals were removed and purified as just described. On recrystallizing from dilute alcohol, the colorless needles melted at 194°-195° (corr.). They were entirely identical with the 2-isobutyl-4-ketodihydroquinazoline prepared from anthranilic acid.

The *picrate* melted at 188.5°-189.5° (corr.). This did not quite agree with the melting-point reported by Gotthelf[1] (192°), but further recrystallization did not change the result given above.

The Preparation of 2-Alkyl-4-ketodihydroquinazolines by the Action of Warm Hydrogen Dioxide Solution upon the Acylanthranilicnitriles.

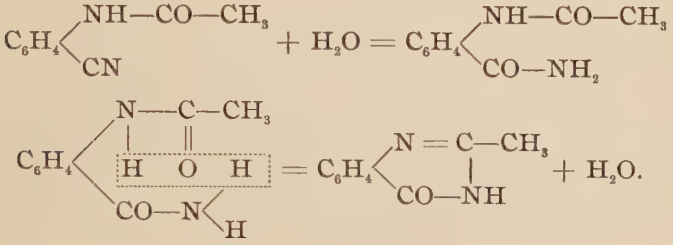
It was shown by Weddige[2] some time ago that the acyl derivatives of anthranilamide can be condensed to the quinazolines by the action of heat and also by acids and by alkalies. Inasmuch as the acyl derivatives of anthranilicnitrile can be obtained, as has been shown already, it was thought that these acylated nitriles could be converted to the corresponding amides by warming gently with potassium or sodium hydroxide solution. The separation of the intermediate acylamide was not contemplated, as under the influence of the alkali, the amide, if formed, should immediately condense to the quinazoline. However, Niementowski[3] has shown that orthoaminoparatolylamide may be prepared by boiling the nitrile in dilute potassium hydroxide solution until the last drop dissolved, when the amide crystallized out on cooling.

In addition to the hydrolyzing effect of the alkali alone it was thought that the addition of hydrogen dioxide would assist in the

[1] Loc. cit.
[2] J. prakt. Chem. (2), 31, 124.
[3] J. prakt. Chem. (2), 40, 10.

reaction, and this idea was tested with excellent results, the alkaline dioxide solution causing the formation of the quinazolines by simply warming the mixture to 40° or 50°.

The following reactions are given as the most probable explanation of this synthesis.



By the action of alkaline hydrogen dioxide, then, it was found possible to prepare the corresponding quinazolines from the acylanthranilicnitriles without the use of sealed tubes and also without separating the intermediate amide. The yield of quinazolines in this synthesis was found to be good and the purification of the crude product very easily accomplished, a single recrystallization being usually sufficient to bring the compound to the proper melting-point. The use of alkali alone or of hydrogen peroxide alone was not as efficient as a combination of the two.

By the use of this method also, the 4-ketodihydroquinazoline itself was obtained, though it could not be prepared by heating formic acid in sealed tubes with anthranilicnitrile.

The compounds obtained were always identical with those prepared from anthranilic acid, its nitrile, or their acyl derivatives.

(1) *4-Ketodihydroquinazoline,* $C_6H_4\langle{}^{N=C-H}_{CO-NH}$.—This was prepared from some of the crude formyl compound mentioned in an earlier part of this paper. The formyl derivative was prepared by boiling anthranilicnitrile and glacial formic acid together for some time and extracting the crystalline, yellow cake with boiling 95 per cent. alcohol. The alcoholic solution is boneblacked for some time, and the warty masses which separated on

concentrating and cooling were several times recrystallized. This still impure product was dissolved in 10 per cent. potassium hydroxide and hydrogen dioxide added in excess. The mixture was then heated for an hour and a half to 40°-50°, and allowed to stand over night. The alkali was neutralized by hydrochloric acid and the solution was made alkaline with ammonia, as the latter alkali does not form salts with the quinazolines. No precipitate was formed by the ammonia water, the quantity present being too small to separate from the volume of solution now obtained. The whole was evaporated to dryness and extracted with 99 per cent. alcohol. By concentrating the alcoholic extract, the quinazoline separated in fairly good condition. A small quantity was very carefully sublimed over a sand-bath, and beautiful white needles were obtained. These crystals melted at 215.5°-216.5° (corr.). Knape[1] gives the melting-point as 211°-212°, though his product was not sublimed. Sufficient quantity for analysis was not obtained.

The *picrate* was prepared from the mother-liquors and recrystallized until the melting-point (203.5°-204.5°, corr.) remained constant.

The methyl, ethyl, *n*-propyl, and isopropyl-4-ketodihydroquinazolines were prepared by this synthesis before this research was undertaken.

(*2*) *2-Isobutyl-4-ketodihydroquinazoline.*—A small quantity of the isovalerylanthranilicnitrile, prepared as already described, was dissolved in 10 per cent. potassium hydroxide solution (25 cc.) and 25 cc. of a 3 per cent. hydrogen dioxide solution added in two portions. The solution was heated to 40°-50° for some time and allowed to stand. The bulky, white precipitate thrown down by ammonia water, after acidifying with hydrochloric acid, was recrystallized from dilute alcohol, when characteristic crystals of the quinazoline separated. These melted at 194.5°-195.5° (corr.).

It may be said that the yield of quinazolines obtained by the use of warm alkaline hydrogen dioxide solution was much better than that resulting from heating the acylanthranilicnitriles in sealed tubes with acid anhydrides.

[1] Loc. cit.

The Action of Potassium Hydroxide Solution Alone on the Acylanthranilicnitriles.

To determine if the quinazoline condensation could be produced by the action of the alkali alone, a quantity of the acetyl-derivative was dissolved in hot water and sufficient concentrated potassium hydroxide added to make the amount present equal to 10 per cent. of the total solution. The mixture was then kept at 40°-50° for over two days. The solution was acidified with hydrochloric acid and neutralized with ammonia, evaporated to dryness and extracted with absolute alcohol. On concentrating the alcoholic extract a small quantity of brownish crystals separated. These were dried and found to melt at 230°-236°. (The methylquinazolone melts at 239°.) The quantity of crystals recovered was too small to purify further, but the results indicate that the alkali, under the conditions of the experiment, had produced a small quantity of the quinazoline. This experiment also illustrates the helpful effect of the hydrogen peroxide solution.

Part II.

The Synthesis of Alkylthioketodihydroquinazolines from Anthranilicnitrile.

A review of the foregoing methods for the preparation of alkylketodihydroquinazolines from anthranilicnitrile will show that these syntheses depend upon the intermediate formation of acyl derivatives of anthranilamide, the quinazoline resulting by the condensation of the amide with the splitting out of water, or, in case of the formation of the acyl-secondary amide, of the fatty acid. Since it has been shown that anthranilicnitrile and fatty acids or fatty acid anhydrides yield the ketodihydroquinazolines when heated in sealed tubes, the possibility of obtaining the corresponding thioketodihydroquinazolines by the use of a thio fatty acid was at once suggested.

It has been pointed out that Weddige,[1] Niementowski,[1] and others have demonstrated that the acylorthoaminobenzamides readily pass over into the quinazolines under the influence of

[1] Loc. cit.

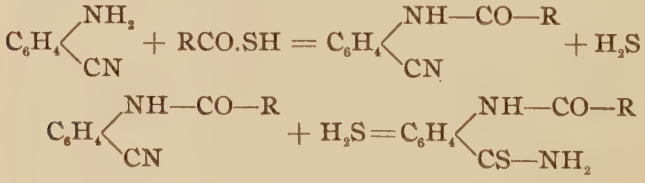
heat, acids or alkalies, and this synthesis also suggested the idea of obtaining the thioquinazolines by a similar condensation of the acyl derivatives of orthoaminobenzthiamide.

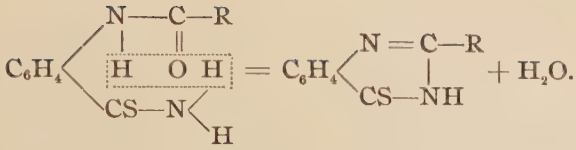
Further, we have already shown that the acylanthranilicnitriles easily yield the quinazolines by treating with a warm alkaline hydrogen peroxide solution, and, therefore, it appeared probable that these acylated nitriles could be made to take up hydrogen sulphide as well as water, giving the corresponding thiamide which would condense, as already shown.

In addition to the above methods which, of course, were brought to mind by the syntheses of the oxygen derivatives of the quinazolines, the idea of carrying out all of the processes in a single operation was developed in the course of the investigation. It was thought to prepare the intermediate acylaminobenzthiamide by heating the *o*-aminobenzonitrile with an acid anhydride and an alkali sulphide. These reacting bodies should produce, first, the acylanthranilicnitrile and then the thiamide by action of the hydrogen sulphide liberated from the alkali sulphide, as will be explained more in detail in a succeeding paragraph.

All of the ideas suggested above were practically tested in the laboratory and all were found to yield excellent results. It follows, then, that the methods heretofore reported for the preparation of alkylketodihydroquinazolines from anthranilicnitrile are now paralleled by similar processes for the production of the alkylketodihydroquinazolines. The various reactions involved in these syntheses are explained on the basis of those that have been suggested in the case of the oxygen derivatives.

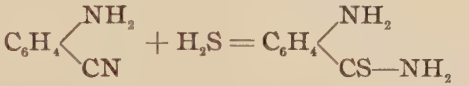
(I) In using thio fatty acids and anthranilicnitrile, the acylated nitrile is first formed and an equivalent of hydrogen sulphide set free. As the process is carried out in a sealed tube, the liberated gas cannot escape, and, when the temperature becomes sufficiently high, it attaches itself to the CN group, forming the thiamide ($-CN + H_2S = -CS-NH_2$), as shown below.

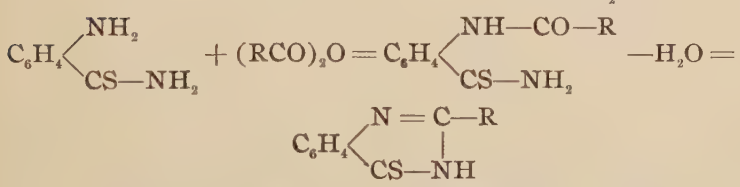




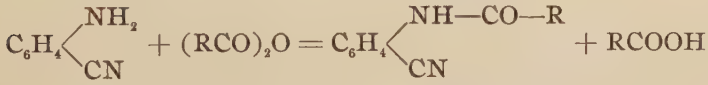
The condensation of the thiamide follows the course of the oxygen amide.

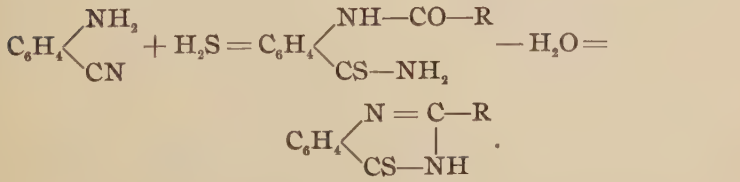
(II) The second synthesis suggested is a modification of the first. In this case the thiamide is first prepared. This can be done quite easily by the action of an alcoholic solution of hydrogen or ammonium sulphide on the anthranilicnitrile, the crude amide thus produced being purified by recrystallizing from carbon tetrachloride, or from water, after washing with carbon bisulphide or tetrachloride. It is an easy matter to obtain the sulphur amide, while we are not yet certain that the oxygen amide can be successfully prepared by the action of acids or alkalies on the anthranilicnitrile. The orthoaminobenzthiamide obtained is heated with acid anhydrides when the thioquinazolines result:



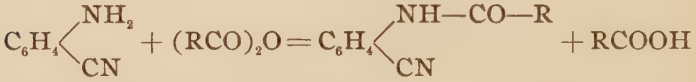


(III) Instead of isolating the thiamide, the acylanthranilicnitriles, prepared as already described, may be heated directly with an alcoholic solution of hydrogen sulphide:

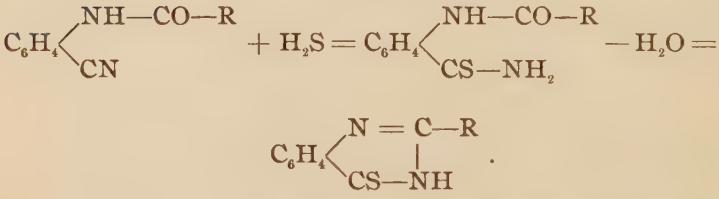




(IV) It has been found that the reactions involved in III may be brought about in one operation, as suggested above, by heating in a sealed tube the aminonitrile, the acid anhydride, and an excess of crystallized sodium sulphide. The anhydride first reacts with the primary amino group with the liberation of the free organic acid which, in turn, sets free an equivalent of hydrogen sulphide. The hydrogen sulphide cannot escape from the tube and the reaction with the cyanogen group then occurs. On raising the temperature, the quinazoline condensation takes place. The entire series of reactions are carried out, therefore, in the tubes.



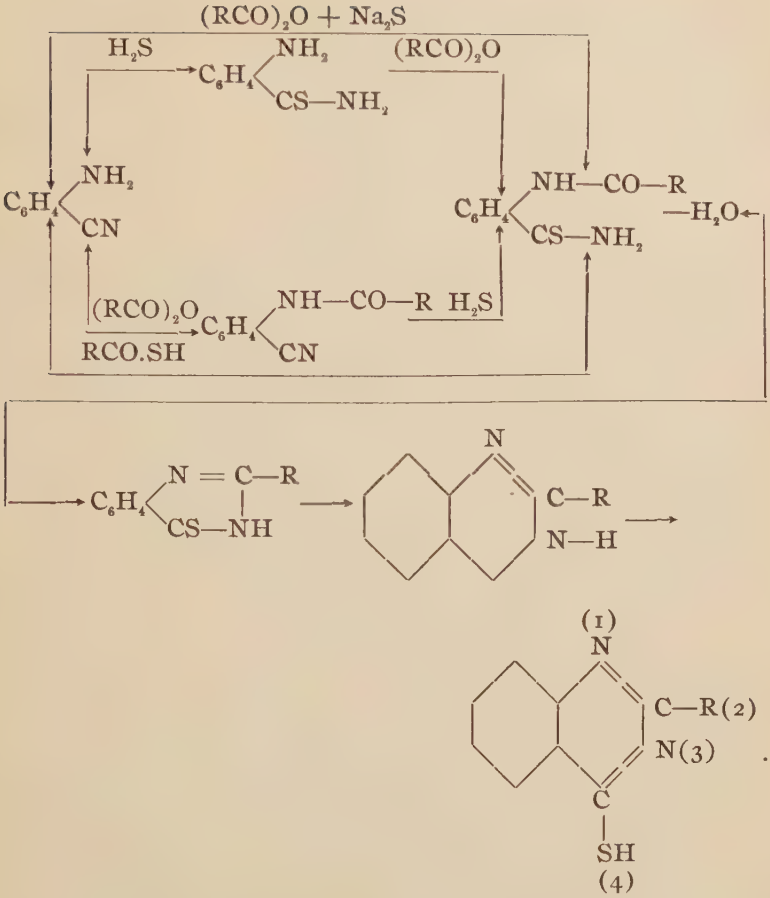
$$2RCOOH + Na_2S = 2RCOONa + H_2S.$$

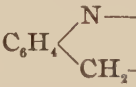


This very rapid method of preparing the quinazolines has proven very satisfactory and its advantages are obvious. It is unnecessary to isolate any of the intermediate products or to use the thio fatty acids which are not always conveniently at hand.

The condensation product from the tube is very easily purified and the yield is also quite satisfactory. The sodium salt of the fatty acid used (being anhydrous) may also assist in the formation of the condensation product.

The relation between these syntheses may be seen by reference to the following diagram:



All of the thioquinazolines described here differ in type from those hitherto prepared,[1] because the sulphur is carried by the carbon atom adjacent to the benzene nucleus, *i.e.*, at position 4 indicated above, while those recorded in the literature have the sulphur attached to the carbon atom between the nitrogens, *i.e.*, at position 2, as in the following compound: 

[1] Compare Stewart: J. prakt. Chem. (2), **44**, 415; Busch: Ber. d. chem. Ges., **25**, 2853; Paal and Commerell: *Ibid.*, **27**, 1866; Paal and Vanvolxem: *Ibid.*, **27**, 2413; Busch and Brunner: J. prakt. Chem. (2), **52**, 373; etc.

In the preparation of the methyl, ethyl, normalpropyl, and isopropyl derivatives by these methods, the condensation product invariably separated in beautiful, golden yellow crystals which were easily purified, as has been stated, and the yields were excellent.

Orthoaminobenzthiamide, $C_6H_4\begin{cases}NH_2\\CS—NH_2\end{cases}$.

—This was prepared by placing anthranilicnitrile in a strong glass tube, adding absolute alcohol and a few drops of ammonia water, saturating with dried hydrogen sulphide and heating at 105°-110° for several hours. It is better to cool the alcoholic solution to 0° while passing in the hydrogen sulphide, though this is not absolutely necessary when ammonia is present. This treatment rarely converts the whole of the nitrile into the thiamide. If the alcoholic solution is concentrated the thiamide may crystallize out in the tube on cooling, and when it separates in this way it is generally in purer condition than when the solution is evaporated in the open air, because, in the latter case, contamination with free sulphur is almost sure to occur. When the crystals do separate in the tube, they may be washed well with ether to remove unchanged nitrile and then recrystallized from water, from which leafy crystals of satisfactory purity are obtained. Care should be exercised that the tube does not extend beyond the furnace, as in this case, the ammonium sulphide will sublime in the forward end. Where no crystals separated in the tube, the alcoholic solution was concentrated and the amide crystallized out in well-formed cubes melting quite sharply at 120° (corr.); but, notwithstanding this fact, these crystals occluded a considerable quantity of free sulphur, as the following analysis will show: Carbon, 50.06 and 49.96; hydrogen, 4.66 and 4.82; sulphur, 26.38 (compare with analysis of pure product).

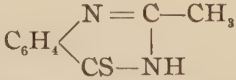
The following procedure was found satisfactory for obtaining a pure product: Transfer the alcoholic solution in the tube to a small beaker and add sufficient cold water to precipitate the unchanged nitrile and the thiamide, filter and dry. Now wash with chloroform to remove the nitrile and once or twice with carbon bisulphide, using small quantities of the latter, as it readily dis-

solves the amide. The dried residue is then crystallized from water, after filtering from the small quantity of insoluble material usually present. Beautiful, light yellow flakes or plates separate out, leaving a mother-liquor of a yellow color. Or, to the alcoholic solution coming from the tube a very slight excess of dilute hydrochloric acid may be added, followed by sufficient water to precipitate most of the unchanged nitrile. To the filtrate containing the hydrochloride of the amide, ammonia is now added to alkaline reaction, and the precipitated body washed and crystallized from water or from a small quantity of chloroform. These methods give a pure compound, melting at 121°-122° (corr.).

The pure thiamide crystallizes in flakes from water and usually in cubes from alcohol. It is soluble with difficulty in water, ether or chloroform in the cold; moderately soluble in the same solvents when boiling, and quite easily soluble in alcohol or carbon bisulphide. The substance softens under boiling water. Some of the carefully purified product was analyzed with the following results: 0.2061 gram substance gave 0.4184 gram carbon dioxide and 0.0994 gram water.

	Calculated for $C_7H_8N_2S$.	Found.
Carbon	55.260	55.36
Hydrogen	5.263	5.31

It is also possible to prepare the thiamide under ordinary pressure, but the results are not so satisfactory as when using sealed tubes and higher temperature and pressure.

2-Methyl-4-Thioketodihydroquinazoline,  .

(*a*) *From Orthoaminobenzthiamide and Acetic Anhydride.*— This compound was prepared by Bogert and Breneman[1] by boiling the thiamide and acetic anhydride, and crystallizing the thioquinazoline thus produced from dilute alcohol. The yield by this method was not very good.

(*b*) *From Acetylanthranilicnitrile and Hydrogen Sulphide.*— This was also prepared by Bogert and Breneman[2] before this work

[1] J. Am. Chem. Soc., 25, 377.
[2] Loc. cit.

was undertaken. The nitrile was heated in sealed tubes at 100° with alcohol saturated at 0° with hydrogen sulphide. A small quantity of ammonia was added to the alcoholic solution. The thioquinazoline crystallized out on cooling and was purified by recrystallizing from 20 per cent. alcohol, the yield being good. The same synthesis was accomplished by heating in an open flask, but the yield was not so satisfactory.

(*c*) *From Anthranilicnitrile, Acetic Anhydride and Sodium Sulphide.*—By heating these substances together in sealed tubes for an hour and a half at 100°-110°, the condensation product was obtained in beautiful crystals and also in good yield. It was found by several experiments that temperatures much above 110° will cause decomposition with blackening. Tubes heated to 160° for sixteen hours, and to 126° for the same period gave no condensation product at all, complete decomposition having taken place. It is also unadvisable to continue the heating longer than two or three hours. The crystalline product obtained from the tube was dissolved in dilute sodium hydroxide solution, filtered and the thioquinazoline precipitated by a current of carbon dioxide.

This quinazoline can be prepared also by boiling the materials together in an open flask, or, better, by heating in an oil-bath to the boiling-point of the mixture. After heating for some time, the contents of the flask set to a cake of yellow crystals. This usually requires about an hour and a half. The crystals so obtained are more impure and are not so easily obtained in good condition as those coming from the tube.

(*d*) *From Anthranilicnitrile and Thiacetic Acid.*—These substances were heated in sealed tubes in the usual manner, the thioquinazoline separating in the tube in good yield. It may be unnecessary in some cases to further purify the tube product.

Properties of the 2-Methyl-4-thioketodihydroquinazoline.—The products obtained from the above reactions were identical in all respects, and crystallized from dilute alcohol in yellow needles or prisms of considerable length, melting at 218°-219° (corr.) with decomposition. By careful heating the substance may be sublimed in yellow needles, and then shows a somewhat higher melting-point (218°-221°, corr.). It dissolves readily in alkalies

and hot alcohol, and is slightly soluble in water, ether, chloroform, or benzene, when hot. Some of the purified product (prepared by Bogert and Breneman) by the action of hydrogen sulphide on acetylanthranilicnitrile was analyzed with the following results:

0.1630 gram substance gave 0.3665 gram carbon dioxide and 0.0692 gram of water.

	Calculated for $C_9H_8N_2S$.	Found.
Carbon	61.364	61.29
Hydrogen	4.546	4.71

The picrate forms large, light yellow needles fusing at 198.5°-199.5° (corr.), and is moderately soluble in cold water, more readily in hot water or in dilute alcohol; easily dissolved by 95 per cent. alcohol.

2-Ethyl-4-thioketodihydroquinazoline, $C_6H_4\begin{cases} N=C-C_2H_5 \\ | \\ CS-NH \end{cases}$.

(*a*) *From Orthoaminobenzthiamide and Propionic Anhydride.*—The thiamide was placed in a strong glass tube and treated with a slight excess of propionic anhydride. The tube warmed up at once, and, as the temperature rose, the amide was completely dissolved. On cooling to the temperature of the laboratory, the product separated on the sides of the tube in colonies of small, rose-like masses, the contents of the tube finally becoming solid. The temperature of the oven was kept at 110°-115° for an hour and a half, and light yellow, cubical crystals were found in the brownish liquid. These crystals were perfectly formed and were apparently quite pure. They were collected and well washed with dilute alcohol, when they showed the proper melting-point (203°-203.5°, corr.) for the thioquinazoline.

(*b*) *From Propionylanthranilicnitrile and Hydrogen Sulphide.*—The pure propionyl derivative was placed in the tube with alcohol, a few cubic centimeters of strong alcoholic ammonia added, and the whole saturated with hydrogen sulphide at 25°. The tube was heated to 156° for sixteen hours. The contents were then brought into solution by dilute caustic alkali and the thioquinazoline thrown out by a current of carbon dioxide. The compound was then crystallized from dilute alcohol.

Another tube gave beautiful, long, yellow crystals, which were washed, dried and found to melt at 200.5°-201.5° (corr.). This low melting-point was not expected, as the product seemed quite pure. Contamination by free sulphur was suspected and an estimation of this element showed this to be a fact (compare with *o*-aminobenzthiamide).

0.2453 gram substance gave 0.3200 gram barium sulphate = 17.50 per cent. The calculated percentage of sulphur is 16.84 per cent. The analysis of the product purified by solution in alkali, etc., shows the compound thus obtained to be pure.

(*c*) *From Anthranilicnitrile, Propionic Anhydride and Sodium Sulphide.*—Two grams of the nitrile, 3.5 cc. of the anhydride, and a considerable excess of sodium sulphide were sealed in a tube and heated to 165°-170° for seven hours. No pressure was evident on opening. The tube contained a solid mass of well-formed crystals which were slightly brown. These were washed with water, dissolved in weak caustic alkali solution, precipitated by carbon dioxide and crystallized as usual. The compound came out in an excellent condition.

This thioquinazoline was prepared also in an open flask. The nitrile, anhydride, and sodium sulphide were brought together in proper proportions, and the flask heated in an oil-bath for one and a half hours to 100°-125°. The contents of the flask did not set to a cake of crystals as in the case of the methyl compound when using this method, though a few yellow crystals separated. On cooling, however, the cake of crystals was obtained as usual. These were dissolved in sodium hydroxide solution and purified in the usual manner. The crude crystals should not be boiled in the alkali, as this caused the separation of gummy matter in one preparation.

Properties of the 2-Ethyl-4-Thioketodihydroquinazoline.—The ethyl derivative forms yellowish needles, melting at about 203°-204° (corr.) with decomposition. In some cases it is difficult to obtain the body melting above 199°-201°, as a very small amount of impurity seems to lower the melting-point considerably. By heating carefully in a gentle current of air or of carbon dioxide it may be sublimed in delicate needles which show a

somewhat lower melting-point (200.5°-201.5° (corr.)). It is apparently insoluble in cold water, moderately soluble in dilute alcohol or in carbon tetrachloride; soluble in alcohol, aniline, benzene, or in caustic alkalies. The purified substance from the sodium sulphide method was analyzed with the following results:

0.2445 gram substance gave 0.5719 gram carbon dioxide and 0.1176 gram water.

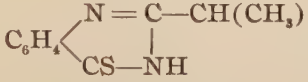
0.1923 gram substance gave 25.9 cc. nitrogen at 25° and 756 mm.

0.1993 gram substance gave 26.8 cc. nitrogen at 25° and 756 mm.

	Calculated for $C_{10}H_{10}N_2S$.	Found. I.	II.
Carbon	63.158	63.79	....
Hydrogen	5.263	5.34	....
Nitrogen	14.737	14.93	14.90

The *picrate* separated in yellow needles, but the quantity available was not sufficient to crystallize to a constant melting-point.

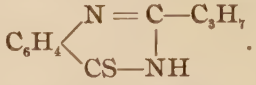
2-Isopropyl-4-thioketodihydroquinazoline.



—Three grams of anthranilicnitrile, 4.5 cc. of isobutyric anhydride, and 4 grams of sodium sulphide were heated to 175° for six hours, and no pressure was found on opening the cold tube. The tube product was dissolved in dilute caustic soda solution and the thioquinazoline thrown out and crystallized in the usual manner. It was found necessary to use about 300 cc. of the dilute caustic alkali solution. To prevent the formation of gummy matter the alkali solution must be warmed over the water-bath only. This quinazoline is much more insoluble in dilute alcohol than the methyl compound. The compound crystallizes in yellow needles of considerable length, which melt at 202°-203° (corr.). It will be noticed that this melting-point is identical with that of the ethyl compound already described. To make sure that no mistake had been made, the preparation was repeated and a product of the same melting-point was obtained. This coincidence can be accounted for by virtue of the fact that

these bodies show a decreasing melting-point with increasing molecular weight, and the iso-compounds melt lower than those of normal structure.

2-Normalpropyl-4-thioketodihydroquinazoline,



—Anthranilicnitrile, *n*-butyric anhydride, and sodium sulphide were heated together in sealed tubes for eight hours at 182°, and the crystalline condensation product purified as described for the isopropyl derivative. It forms light yellow needles, which melt at 182°-183° (corr.), and may be sublimed in a gentle current of air or carbon dioxide if heated carefully.

Part III.

3,5-Dibrom-2-aminobenzoic Acid, Its Nitrile, and Some Quinazolines Prepared from the Latter.

Up to the present time no ketodihydroquinazolines carrying halogen on the benzene nucleus have been recorded, those hitherto reported having been prepared usually by the action of a phosphorus halide on the keto-body, or by attaching a halogen substituted side-chain to the nitrogen ring. Inasmuch as the quinazolines may be obtained from anthranilicnitrile by a number of methods, it seemed desirable to determine if it were possible to prepare in sufficiently good yield and purity a halogen substitution product (preferably a bromine compound) of the aminonitrile in the hope of obtaining, ultimately, the halogen keto and thioketodihydroquinazolines by employing processes described in preceding pages. The possibility of introducing halogen into the anthranilicnitrile by some method which would not give a mixture of isomers troublesome to separate, once established seemed to give promise of a method of wide application for obtaining the compounds sought. With this idea in view, the research upon these compounds was now turned in this direction, and it will be shown that the method finally worked out for brominating anthranilicnitrile leaves little to be desired, the yield of the pure product being practically quantitative, and no isomeric bromine compounds being simultaneously produced.

In the course of this work the 3,5-dibrom-2-aminobenzonitrile was prepared and carefully purified, but this nitrile gave, on saponification, an acid which did not agree in melting-point with any of the 3,5-dibromanthranilic acids recorded in the literature. The location of the bromine atoms in the nitrile itself was not only a matter of some difficulty, as will be explained, but the wide difference in the melting-point of its acid with that of previous investigators furnished an additional problem for solution.

The method of obtaining the 3,5-dibromaminobenzonitrile having been developed, it was now applied to the anthranilic acid itself with the view of producing the same dibromanthranilic acid as obtained by saponifying the nitrile already prepared. After a number of attempts, compounds with similar melting-points were obtained, and the bromine atoms were shown to occupy the same relative positions with respect to amino and carboxyl groups in the acid as to the amino and cyanogen groups in the nitrile. In view of the results which follow, it seems safe to say that the pure 3,5-dibrom-2-aminobenzoic acid was not in the hands of Hübner,[1] who reduced the 3,5-dibromnitrobenzoic acid by tin and hydrochloric acid. Hübner found a melting-point of 225°, which was the same as that reported by him for the 3,4-acid, while Dorsch[2] states that 3,4-acid melts at 226°-228°, the compound prepared by him agreeing with that obtained by Smith.[3]

It will be shown later, however, that the proper melting-point for the 3,5-dibrom-2-aminobenzoic acid is 235°-236° (corr.).

Previous attempts to brominate anthranilic acid directly have generally resulted in the formation of tribromaniline, but it will be shown that by using the *calculated* quantity of *nascent* bromine on the hydrochloric acid salt of anthranilic acid the 3,5-dibrom acid is very readily produced. The crude product thus obtained must be bone-blacked and purified by repeated crystallization of the sparingly soluble barium salt. No isomeric bromine compounds are formed. However, it is often somewhat tedious to secure a body of constant melting-point, a small quality of impurity having the effect of lowering the fusing-point considerably.

The positions of the bromine atoms in the molecule were de-

[1] Ann. Chem. (Liebig), **222**, 175.
[2] J. prakt. Chem. (2), **33**, 36.
[3] Ber. d. chem. Ges., **10**, 1706.

termined by eliminating the amino group by the diazo reaction, and purifying the dibrombenzoic acid thus obtained, but the usual method of producing the diazonium salts cannot be applied in this case.

The bromine used in the following work was liberated (in the solution of the compound to be brominated) as shown by the following reaction:

$$5KBr + KBrO_3 + 6HCl = 3Br_2 + 6KCl + 3H_2O.$$

The potassium bromide-bromate solution was made of such a strength that 1 cc. = 0.0800 gram bromine when acidified.

Quite a number of experiments were carried out with anthranilic acid to determine the conditions of best yield. In brominating by use of the above mixture, exactly 4 atoms of bromine must be liberated for each molecule of acid used, as it was found by experiment that the anthranilic acid is entirely converted into 2,4,6-tribromaniline by excess of bromine. It is rather better to use a slight deficiency of bromine, thus avoiding the formation of tribromaniline, the unchanged chloride of the acid being easily removed by washing with water slightly acidified by hydrochloric acid. To prevent the formation of hydrobromic acid, sufficient potassium bromate may be used to liberate all of the bromine, and, in this case, it is necessary, of course, to use only two atoms of bromine to a molecule of anthranilic acid.

Bromination of Anthranilic Acid.—Fifty grams of anthranilic acid are dissolved in 2 liters of water and 125 cc. concentrated hydrochloric acid added, followed by the gradual addition of the brominating solution. The bibrom-compound separates at once in a voluminous, flocculent precipitate usually light brown in color, but sometimes possessing a faint bluish cast. It is unnecessary to keep the temperature down by adding ice, nor is the purity of the product influenced by the dilution, as the same result was obtained in carrying out the preparation at a volume of 18 liters. After standing for an hour the crude acid is separated and well washed, transferred to a large porcelain dish, containing boiling water, and made faintly alkaline with a hot concentrated solution of barium hydroxide. The excess of caustic barium is then re-

moved by passing a rapid stream of carbon dioxide, and the boiling-hot solution of the barium salt passed through a folded filter in a hot-water funnel. On cooling, the crude barium salt separates in well-formed, light brown crystals. These are separated from the mother-liquor, dissolved in the minimum quantity of hot water, decomposed by hydrochloric acid, and the precipitated, brown dibromanthranilic acid bone-blacked in alcoholic solution for several hours, using a considerable quantity of char. The alcohol is distilled off in part and the concentrated solution poured into cold water, and the precipitated acid again converted into the barium salt. It may happen that it will be found necessary to decompose and bone-black a second time. After recrystallizing several times, the barium salt will be obtained in pure condition, and from this the free acid is prepared and crystallized from alcohol or benzene.

Properties of 3,5-Dibrom-2-aminobenzoic Acid.—When prepared as directed above, the acid separates from alcohol in small, needle-like prisms usually retaining a light yellowish color. When very carefully purified by recrystallizing from benzene, white prisms may be secured. From the latter solvent, the body separates on the rod and sides of the beaker in small crystals, which are easily soluble in absolute alcohol, ether or in acetone; quite easily dissolved by 95 per cent. alcohol; moderately soluble in cold benzene and toluene, but quite soluble on boiling; insoluble in ligroïn and almost insoluble in cold or hot water. To obtain crystals of even moderate size, the solutions of the acid must be cooled very slowly over the water-bath. Alcoholic solutions darken readily when boiled for any length of time.

The melting-point of the compound crystallized from alcohol and from benzene was 235°-236° (corr.)

A nitrogen determination gave the following result: 0.3330 gram gave 14.40 cc. nitrogen at 23° and 758 mm.

	Calculated for $C_6Br_2H_2\langle^{NH_2}_{COOH}$.	Found.
Nitrogen.....	4.74	4.90

Barium Salt, $\left(C_6H_2Br_2\langle^{NH_2}_{COO}\right)_2$ Ba.$3\frac{1}{2}H_2O$.—The barium salt

was prepared as already described and air-dried for two days after pressing between folds of filter paper, and the water of crystallization determined.

0.6942 gram dried five hours at 100° lost 0.0548 gram water.

	Calculated for $(C_7H_4Br_2N)_2Ba.3\frac{1}{2}H_2O$.	Found.
H_2O	7.99	7.89

Hübner[1] reports this salt as containing 4 molecules of water of crystallization.

Another sample of the air-dried salt was placed in a desiccator over sulphuric acid for about thirty-six hours and the water of crystallization determined.

0.5618 gram salt lost 0.0269 gram water on drying five hours at 100°.

0.6186 gram salt lost 0.0313 gram water.

	Calculated for $(C_7H_4Br_2N)_2Ba.2H_2O$.	Found. I.	Found. II.
H_2O	4.73	4.78	5.05

It is seen, therefore, that the salt retains 2 molecules of water when dried over concentrated sulphuric acid. The samples were dried to constant weight, and the following determinations of barium show that the rest of the water was expelled at 100°:

0.5349 gram of dried salt gave 0.1697 gram $BaSO_4$.

0.5873 gram of dried salt gave 0.1876 gram $BaSO_4$.

	Calculated for $(C_7H_4Br_2N)_2Ba.2H_2O$.	Found. I.	Found. II.
Barium	18.00	17.76	17.83

The sodium and potassium salts separate from water in needles, and, in small quantity, cannot be washed with alcohol or water on account of their great solubility.

Location of the Bromine Atoms.—This was done by eliminating the primary amino group and comparing the compound thus produced with the dibrombenzoic acids previously prepared. On account of the accumulation of negative elements on the ring, the amino group was found very difficult to diazotize, the ordinary methods proving worthless. The following procedure, however, gave good results, and the pure 3,5-dibrombenzoic acid was prepared thereby:

[1] Loc. cit.

The brominated anthranilic acid is dissolved in dry alcohol, and
added over a water-bath under a return condenser, while the
vapours of nitrogen (from ammonium nitrite and nitric acid) are
passed into the flask by means of a small tube inserted through
the upper tube of the condenser. The gases are passed in for
some time, the solution in the flask being kept at boiling. The
liquid soon assumes an amber colour, and the tube through which
the gases are passed is very apt to become stopped as the reaction
proceeds. The hot solution is then poured into twice its volume
of cold water, and the light yellow, flocculent precipitate collected
and washed. The body is now purified by pounding the barium
salt, decomposing this salt with mineral acid, and boiling the
liberated acid with several quantities of ether until the aqueous
solution is reasonably clear. This latter result may be difficult to
obtain as the oxides of nitrogen have been passed through the solu-
tion for (say) a time. After shaking a solution of the
barium salt in acids prepared and recrystallised several times, or
until the crystals are white. These are then decomposed by
hydrochloric acid and the precipitated acid well washed, dried and
crystallised from benzene, from which solvent the pure acid separ-
ates in beautiful long needles radiating from a centre. These
are always very slightly yellow, even when the ferrocyanic acid pre-
pared by decomposing the barium salt is perfectly white. The
pure compound melts at 225° 226° (corr.).

Bougault gives a melting point of 222°-227° for 3,5 dibrom-
benzoic acid, while Claus and Wolf assign the body as melting at
218°, and Hübner[3] found 213°-214°.

Barium Salt. $(C_6H_2Br_2(NH_2)CO_2)_2Ba + 3H_2O$.—The barium salt
crystallises in needles from a water solution. It is more insoluble
than the same salt of the amino acid. Some of the carefully puri-
fied crystals were air-dried and analysed with the following re-
sults:

0.4848 gram lost 0.0685 gram water on drying to constant
weight at 105°.

0.4163 gram gave 0.1456 gram barium sulphate.

1 Ann. Chem. (Liebig), 158, 50.
2 Ibid., 269, 224.
3 Ibid., 222, 271.

	Calculated for $(C_7H_3Br_2O_2)_2Ba.3\frac{1}{2}H_2O$.	Found.
H_2O	8.31	8.58
Ba	18.07	18.03

Bromination of Anthranilicnitrile.

In Carbon Tetrachloride Solution.—A quantity of the nitrile was dissolved in carbon tetrachloride and solution of bromine in the same solvent added gradually. An immediate white precipitate (apparently amorphous) was thrown out. This compound melted poorly at 195°-200° and showed a peculiar conduct on crystallizing from 95 per cent. alcohol. On boiling up with the alcohol, the entire mass first liquefied on the bottom of the flask as an oily layer which disappeared on further boiling. On account of the high melting-point, this was somewhat surprising. On cooling the alcoholic solution, white needles of considerable length separated and these were found to melt sharply at 95.5° (corr.). This body was reserved for further investigation. Bromination was also tried in aqueous and in benzene solution with apparently the same result.

Bromination with Hypobromite Solution.—The plan of using nascent bromine was first carried out by liberating the latter element from a solution of sodium hypobromite by acidifying with hydrochloric acid. To 3 grams of the nitrile in dilute alcoholic solution hydrochloric acid was added in considerable excess, and freshly prepared sodium hypobromite was then added slowly. Sufficient of the brominating mixture was added to form a dibrom substitution product. Very small, and perfectly white, feathery needles separated at once. These were recrystallized from alcohol (95 per cent.) and were found to melt at 156°-156.5° (corr.). A quantity carefully sublimed gave exactly the same melting-point. The yield seemed to be excellent, and some of the purified product was analyzed with the following results:

0.2387 gram gave 22.90 cc. nitrogen at 29° and 754 mm.

0.2463 gram gave 0.3342 gram silver bromide.

	Calculated for $C_6H_3Br_2\langle^{NH_2}_{CN}$.	Found.
Nitrogen	10.15	10.38
Bromine	58.00	57.73

The body at hand was thus shown to be the dibrom derivative of the nitrile. The reaction proceeded very smoothly and no isomeric-bromine substitution products were formed. The yield was good and the compound was obtained in excellent condition and constant melting-point by a single crystallization from alcohol.

To determine if a mono and also tribrom compound could be produced by the same process, the experiment was repeated, using sufficient quantities of the alkaline hypobromite to give the bodies mentioned. In both trials, however, it was found that only a dibrom substitution product was formed, an excess of unchanged nitrile remaining in the first case and an excess of bromine in the latter. The dibrom body is almost insoluble in very dilute alcohol and also in water, and it begins to separate as soon as a few drops of hypobromite are added.

Bromination with a Mixture of Potassium Bromide and Bromate.—To obviate any tendency toward saponification by the alkaline hypobromite, and also to secure an accurate brominating agent, a solution of potassium bromide and bromate was used, which, on acidifying, liberated bromine as shown on page 52. In earlier work the solution of the nitrile was very dilute and the temperature was kept down by adding ice, though these precautions were shown to be entirely unnecessary when the dibrom nitrile was found so difficult to saponify by concentrated hydrochloric acid.

The following process will give a pure dibromanthranilicnitrile in an almost quantitative yield: Ten grams of the nitrile are dissolved in 100 cc. 95 per cent. alcohol and 50 cc. of concentrated hydrochloric acid added. The volume is then brought to 2 liters (add a little more hydrochloric acid if the nitrile shows a tendency to separate), when the brominating solution is added in a fine stream, using a mechanical stirrer if convenient. The voluminous precipitate is washed thorougly on a large fluted paper (cannot be washed by using suction) and pressed out. The mass is now dissolved in the smallest possible quantity of strong alcohol, and water heated to 80° added to the hot alcoholic solution until the cloud produced dissolves with difficulty. The solution is then allowed to cool slowly on the water-bath, when practically all of

the dibromaminonitrile will separate in coarse needles of considerable length. These are generally slightly colored if bone-black has not been used; but, when once recrystallized from alcohol, the compound will be found pure, melting at 156°-156.5°.

Saponification of the Dibromaminonitrile.

Action of Caustic Alkalies.—The dibrom compound having been obtained in considerable quantity, it was thought that the positions of the bromine atoms would be indicated by conversion to the corresponding dibromanthranilic acid, and caustic potash solution was first used for this purpose.

Solutions of various strengths were tried without success. Even very concentrated alkali and long boiling seemed to have practically no effect whatever on this nitrile. When fused gently with potassium hydroxide (with a small quantity of water), the nitrile was decomposed, a yellow product remaining.

Action of Hydrochloric Acid.—The use of alkalies was therefore abandoned, and a quantity of the nitrile was boiled under a return condenser for several hours with concentrated hydrochloric acid. It was very surprising to find that this treatment was without effect upon the nitrile, as the latter compound did not dissolve appreciably, and was recovered unchanged.

Concentrated hydrochloric acid and the nitrile were then placed in a strong tube and heated to 180° for several hours. Under these conditions of temperature and pressure, the acid saponified the nitrile only partially, and no satisfactory results could be secured.

Action of Sulphuric Acid.—Concentrated sulphuric acid charred the nitrile, but dissolved it completely on warming gently, and, after several experiments, it was found that 75-80 per cent. acid would give a fairly satisfactory saponification product, but the color of the acid thus produced was always light brown.

To regulate the temperature 75 per cent. sulphuric acid and the nitrile were heated for several hours to 180° in a sealed tube, when almost perfect saponification took place. In using this method it is necessary to have the tube several inches shorter than the furnace, as the nitrile may sublime out of the acid and thus escape

saponification. The tube should be turned from time to time to insure contact of the reacting bodies, and the temperature should not be allowed to rise above 185° because of the decomposition which then sets in.

The dibromanthranilic acid thus produced was purified by pouring the contents of the tube into a considerable volume of water and recrystallizing the flocculent mass from alcohol, when clear needles melting at 235.5°-236° (corr.) were obtained. The melting point of the crystals did not change on subliming or on recrystallizing. Several preparations were made, the same product being obtained in each case. The melting-point also did not correspond, even approximately, to that reported for any of the dibrom 2-aminobenzoic acids, and this was difficult to explain, since the acid above described was prepared from the pure nitrile, and was itself evidently a pure product as indicated by its sharp melting-point and crystalline condition. This method of brominating the nitrile was now applied to the anthranilic acid itself and the *same* dibromanthranilic acid produced, as has been already explained. Inasmuch as the bromine atoms in this dibrom acid were shown to occupy positions 3 and 5 on the nucleus, it seemed justifiable to conclude that nascent bromine, applied as described to anthranilicnitrile produces 3,5-dibrom-2-aminobenzonitrile. The potassium, sodium and barium salts were prepared from the dibromanthranilic acid obtained by each method, and these compounds were also identical.

Conversion of 3,5-Dibromanthranilicnitrile into 3,5-Dibrombenzonitrile, and 3,5-Dibrombenzoic Acid.—In confirmation of the positions of the bromine atoms in the nitrile, an attempt was made to eliminate the amino group as in the case of the dibrom acid.

Sodium nitrite and hydrochloric acid had no effect whatever, and a number of experiments were made using an alcoholic solution of ethyl nitrite as a diazotizing agent, though no satisfactory results could be obtained. The action of ethyl nitrite is difficult to explain; for, when added in slight excess to an acidulated alcoholic solution of the dibrom nitrile, no diazotizing occurs, but the same solution boiled with a large quantity of a 15 per cent. solution of ethyl nitrite gave an impure product which could not be brought

to a constant melting-point. On evaporating the alcoholic liquors to dryness, a yellowish brown mass remained, smelling strongly of the nitrite. A quantity of this sublimed over boiling water melted at 87°-88°, and when heated in a small beaker over an asbestos disk, long, beautiful needles were obtained melting at 59°-59.5° (corr.), the melting-point of the sublimate rising steadily with the progress of the sublimation, and the crystals throughout retaining a very penetrating odor.

The dibrom nitrile was then dissolved in absolute alcohol and the oxides of nitrogen (from arsenious oxide and nitric acid) were passed in, the arrangement of the apparatus being the same as in diazotizing the dibromanthranilic acid. After passing the gases for some time, the reddish brown liquid in the flask was poured into water and the precipitated, impure product filtered off and dried over sulphuric acid. The alcoholic solution may be evaporated to dryness with advantage, though dibrombenzonitrile is volatile with the vapors of the alcohol. When thoroughly dry, the crude product is sublimed over a water-bath in a gentle current of air or carbon dioxide, when very pretty, clear needles melting at 96.5°-97° (corr.) are obtained. This work was repeated a number of times and the same product secured in each case. The yield, however, of the impure compound is very small, and no solvent was found from which a small quantity could be crystallized.

Claus and Weil[1] report the melting-point of 3,5-dibrombenzonitrile as 89° (uncorr.).

Saponification of Dibrombenzonitrile.—The nitrile obtained as described above (melting at 96.5°-97°) was saponified by heating in a sealed tube with sulphuric acid (75 per cent.) for two hours at 170°. A short tube must be used as the nitrile readily sublimes out of the acid, and it must be turned in the furnace at intervals to insure the contact of the two substances. On cooling, beautiful, clear, hair-like needles were found in the tube. These seemed to be pure, but a melting-point determination showed that it was necessary to separate the small quantity of unchanged nitrile carried by them. This was done by dissolving in dilute caustic soda solution, filtering, decomposing the solution of the sodium salt by acidifying with hydrochloric acid, and recrystallizing from

[1] Ann. Chem. (Liebig), 269, 223.

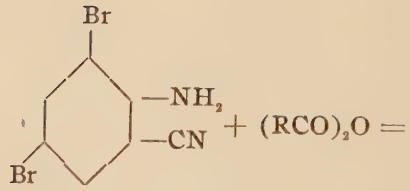
alcohol. Small, clear, well-formed needles were obtained, which melted at 215°-218° (corr.). The entire process was repeated and crystals softening at 215° and melting at 218.5° were secured. These crystals may be whitened (when charred in saponifying) by crystallizing from concentrated sulphuric acid in which they dissolve readily on warming and separate out unchanged on cooling. On account of the difficulty of preparing the nitrile, only a small quantity of the above acid could be obtained and it could not be recrystallized to constant melting-point. The results show unmistakably the 3,5-dibrombenzoic acid obtained from the nitrile to be identical with that prepared from 3,5-dibromanthranilic acid.

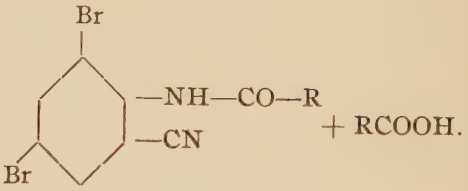
In view of the above results, there is evidently no doubt in regard to the positions of the bromine atoms in the brominated nitriles and acids under investigation.

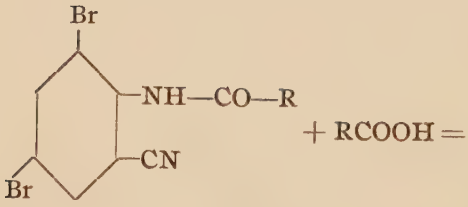
The work has shown that both anthranilicnitrile and anthranilic acid may be brominated by nascent bromine, and also that the positions of the bromine atoms in each compound are the same; that the same dibromanthranilic acid is formed by the saponification of the nitrile as by direction bromination of the acid; that the same dibrombenzoic acid may be obtained from the dibromanthranilicnitrile and the dibromanthranilic acid by the elimination of the amino group in each, and that the proper melting-point of 3,5-dibromanthranilic acid is 235°-236° (corr.) and that of 3,5-dibrombenzoic acid, 219°-220° (corr.) and not as heretofore reported.

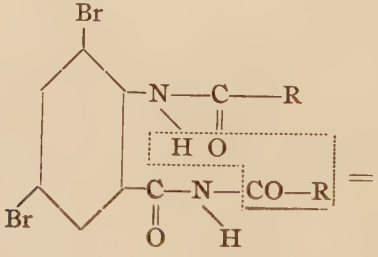
The Synthesis of 6,8-Dibrom-2-alkyl-4-ketodihydroquinazolines.

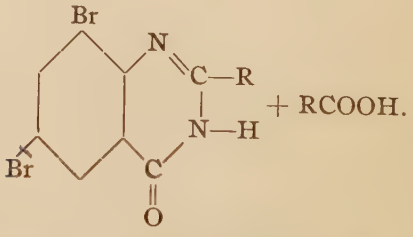
The preparation of quinazolines from the dibromanthranilicnitrile depends upon the reactions already discussed except in this case the intermediate acyldibromanthranilicnitriles cannot be isolated. The introduction of two negative atoms into the molecule so far destroys the basic character of the amino group that it no longer reacts with acid anhydrides at their boiling-points. When placed in sealed tubes and heated to a higher temperature and under pressure, however, these acyl derivatives probably have momentary existence, but under these conditions the quinazoline condensation takes place at once:







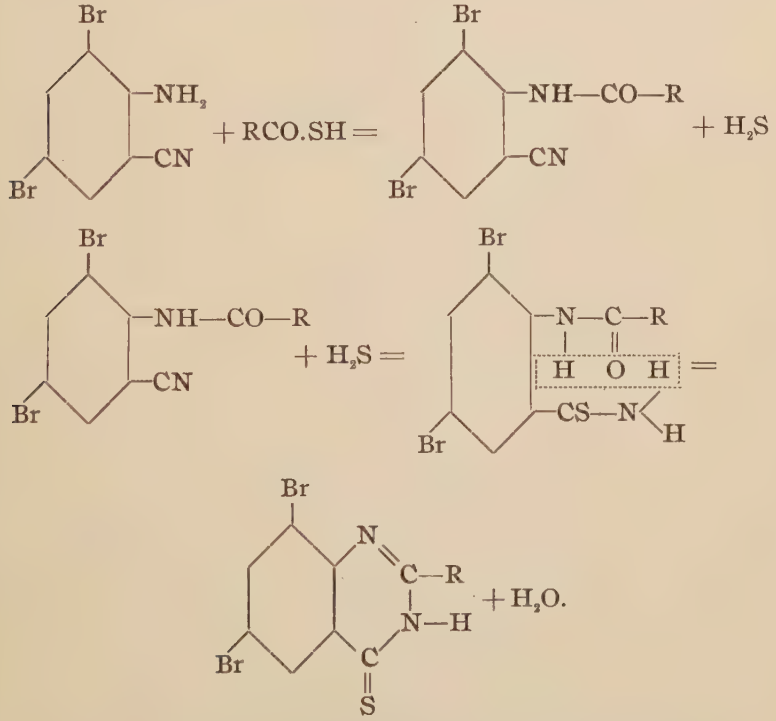




The 3,5-dibromanthranilicnitrile and anthranilicnitrile show a somewhat different deportment towards formic acid when heated with it in a sealed tube, the unsubstituted yielding no condensation product, whereas the brominated nitrile gives an excellent yield of

the 6,8-dibrom-4-ketodihydroquinazoline under the same conditions. In fact, this compound is more easily obtained in good yield than any of its homologues.

The 6,8-dibrom-2-methyl-4-thioketodihydroquinazoline was also produced in very good yield by heating thiacetic acid with the brominated nitrile, though the corresponding oxygen compound was somewhat difficult to obtain at all. It, therefore, seems quite probable that the thio fatty acids react with the amino group with greater ease than the acids or their anhydrides, the hydrogen sulphide liberated reacting with the cyanogen group to produce the thiamide as usual:



While all attempts to prepare ethers of the thioquinazolines resulted unsuccessfully the dibromthioquinazolines do yield the ethers with ease. On the other hand, the brominated bodies do not appear to combine with the mineral acids at all, though the salts of the unsubstituted quinazolines are readily formed. The

alkali salts of the dibrom compounds also seem to be more insoluble in water than the similar salts of those containing no bromine. Another peculiar property of the dibrom quinazolines is found in their deportment toward ordinary solvents in which they are either insoluble or dissolve only sparingly. Aniline dissolves all of them on heating and allows an almost complete separation on cooling; it was used, therefore, in crystallizing all of the brominated quinazoline prepared. The solvent is easily and effectually removed from the crystals by washing with alcohol.

6,8-Dibrom-4-ketodihydroquinazoline, $C_6H_2Br_2\begin{cases} N=C-H \\ \quad\quad | \\ CO-NH \end{cases}$.—

While the formyl derivative of the dibrom nitrile could not be obtained, the above quinazoline resulted in good yield when 3 grams of the nitrile and 3.5 cc. of glacial formic acid were heated to 200°-209° for sixty-nine consecutive hours. After this period of heating the tube was found under heavy pressure, the contents consisting of a mass of yellowish crystals in a small quantity of dark-colored liquid. The whole was transferred to a beaker and washed well with alcohol. The crystals, now somewhat lighter in color, were dissolved as far as possible in about 300 cc. of dilute caustic soda solution, and carbon dioxide passed into the cold liquid until the precipitation of the light yellow quinazoline body was complete. The amorphous mass was separated and thoroughly dried, and crystallized from aniline, using as small a quantity as possible. On cooling, the solution deposited a plentiful quantity of small, clear needles which were thoroughly washed with alcohol and dried.

A second tube containing the same charge as above was heated to 225°-235° for five hours. Heavy pressure was found when the cold tube was opened. The contents were almost black, and only a small quantity of the quinazoline was obtained on treating as described above. Notwithstanding the high temperature withstood by these compounds, it was evident that a satisfactory condensation could not be secured at 235°.

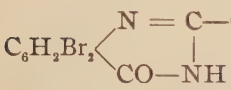
The pure dibrom quinazoline does not melt, but decomposes careful heating in a gentle current of air. A determination careful heating in a gentle current of air. A determination of

of nitrogen in the dried compound gave the following result:

0.2296 gram substance gave 18.5 cc. nitrogen at 25° and 761 mm.

	Calculated for $C_8H_4N_2OBr_2$.	Found.
Nitrogen	9.21	9.00

6,8-Dibrom-2-methyl-4-ketodihydroquinazoline,



.—For some reason, yet unaccounted for, this compound was found to be more difficult to prepare than any other member of the series. A number of experiments were made in which the temperature and period of heating were varied between wide limits, though the yield of the purified compound was always small, and, in not a few cases, practically no condensation product was obtainable.

Two grams of the nitrile and 2 cc. of acetic anhydride were heated to 220°-230° for six hours. The tube was opened and boiled out several times with alcohol, and the crystalline mass ground up with dilute soda solution, and, after warming and filtering from insoluble materials, the quinazoline appeared as a snow-white precipitate on passing in carbon dioxide. This was separated and crystallized from aniline, when slightly colored, small needles were obtained.

This quinazoline is practically insoluble in alcohol, benzene, ligroïn, or 50 per cent. acetic acid; slightly soluble in hot glacial acetic acid, insoluble in cold; moderately soluble in caustic soda and potash solution; almost insoluble in cold aniline, but readily soluble on warming. The compound decomposes when heated slowly to 300°. When quickly heated, it begins to darken very rapidly at 315° and finally melts at 329°-331°. It may be sublimed when carefully heated in a current of air, though a good portion is always lost by decomposition. While dissolving moderately in hot glacial acetic acid, it cannot be successfully recrystallized from this solvent.

The dried crystals separating from aniline were analyzed with the following results:

0.2111 gram substance gave 17.4 cc. nitrogen at 25° and 756 mm.

0.2601 gram substance gave 0.3058 gram silver bromide.

	Calculated for $C_9Br_2H_6.N_2O$.	Found.
Nitrogen	8.80	9.14
Bromine	50.31	50.03

6,8-Dibrom-2-methyl-4-thioketodihydroquinazoline,

$C_6H_2Br_2\begin{cases} N = C—CH_3 \\ CS—NH \end{cases}$.—It has been stated already that this thioquinazoline came out in much better yield than the corresponding oxygen compound, the thio fatty acid evidently reacting with the amino group of the nitrile with greater ease than the acid anhydrides. As the thio acids are not difficult to prepare, the method affords a very convenient means of passing to the sulphur derivatives of the dibrom quinazolines. In addition to this, it also seems quite probable that these thio bodies could be easily produced by heating the dibrom nitrile with sodium sulphide and the acid anhydrides in the manner described in Part II. However, this has not been investigated as yet.

Two grams of the nitrile were placed in the tube with an excess of thiacetic acid and heated to 220°-230° for about six hours. Considerable pressure was found on opening, and the tube contained a beautiful yellow, crystalline condensation product. This was ground up with dilute soda solution, warmed, cooled, and filtered, and the compound thrown out with carbon dioxide in the usual manner. After drying and recrystallizing from aniline, perfectly formed, yellow needles were obtained. This preparation was repeated several times with more or less success in each instance; but, in later experiments to determine the conditions of best yield, it was found that 180° is sufficient to produce the condensation. At this temperature practically no decomposition takes place and a good yield is assured. In one case 3 grams of the dibrom nitrile gave 2.1 grams of the pure, recrystallized thioquinazoline, a yield of 70 per cent.

The solubility of the compound differs very little from that recorded for the oxygen derivative. Hot glacial acetic acid dis-

solves it very sparingly. The compound sublimes slowly when heated with care; decomposes gradually at 290° and does not melt when heated to 350°, but decomposes rapidly.

Complete Analysis.—While the nitrogen and bromine can be easily determined in the usual way, an accurate estimation of carbon and hydrogen is a matter of some difficulty. The high percentage of bromine in these bodies makes it necessary to use every precaution to protect the absorption train from the halogen. A good deal of time was spent in attempting to work out the conditions for a satisfactory combustion for both the sulphur and oxygen derivatives of the methyl compound.

The combustion tube was filled with pellets of a mixture of lead chromate and red lead. The former was prepared from lead acetate and thoroughly mixed wet with the red lead, made into small balls which were dried and heated in an open dish, and finally thoroughly burned out (in the tube) in a stream of dry oxygen. Prepared in this way, the pellets do not disintegrate nor fuse into the tube. Approximate results were obtained by filling the tube in the following way:

(1) An oxidized copper spiral; (2) a long porcelain combustion boat with the substance mixed with dry red lead and covered with a thin layer of red lead; (3) a short silver spiral; (4) the oxidizing mixture; (5) a longer silver spiral; (6) a reduced copper spiral. Sulphuric acid and soda-lime were used to absorb the water and carbon dioxide.

0.2933 gram gave 0.3520 gram carbon dioxide and 0.0536 gram of water.

0.2275 gram gave 0.2748 gram carbon dioxide and 0.0425 gram of water.

0.2069 gram gave 16.40 cc. nitrogen at 27° and 756 mm.

0.2791 gram gave 20.90 cc. nitrogen at 23° and 768 mm.

0.2011 gram gave 0.1483 gram barium sulphate.

0.2295 gram gave 0.2578 gram silver bromide.

	Calculated for $C_9H_6Br_2N_2S$.	Found. I.	Found. II.
Carbon	32.33	32.85	32.94
Hydrogen	1.80	2.03	2.07
Sulphur	9.58	9.64	....
Bromine	47.91	47.79	....
Nitrogen	8.38	8.70	8.52

The combustion must be carried out at as low a temperature as possible, and the forward end of the tube should never be allowed to rise above a dull red heat.

6,8-Dibrom-2-ethyl-4-ketodihydroquinazoline,

$C_6H_2Br_2\begin{cases} N = C—C_2H_5 \\ CO—NH \end{cases}$.—Three grams of dibromanthranilicnitrile and 3 cc. of propionic anhydride were heated to 200° for ten and a half hours and then to 210° for five and a half hours more. The contents of the tube were somewhat dark and gave evidence that the long heating above 200° had brought about some decomposition. The yield also was not very good. The cold tube was under practically no pressure. The product was treated with caustic alkali and precipitated and crystallized as described in the previous preparations, the quinazoline separating in long, white, hair-like needles, melting at 278°-280° (corr.). It will be noted in comparison that the corresponding methyl derivative decomposes slowly at 290°-300°, and melts poorly at 329°-331°. The melting-points decrease gradually with increased molecular weight. An estimation of nitrogen in the dried crystals gave the following results:

0.2148 gram substance gave 15.90 cc. nitrogen at 27° and 755 mm.

	Calculated for $C_{10}H_8Br_2N_2O$.	Found.
Nitrogen	8.43	8.10

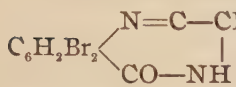
6,8-Dibrom-2-normalpropyl-4-ketodihydroquinazoline,

$C_6H_2Br_2\begin{cases} N = C—C_3H_7 \\ CO—NH \end{cases}$.—Three grams of the nitrile and 3 cc. normalbutyric anhydride were heated to 200° for ten and a half hours and at 210° for five and a half hours. There was no pressure in the cold tube. The crystalline condensation product was treated with alkali and carbon dioxide as usual. The crystals separated from aniline in white, microscopic needles, which appear to be an amorphous powder to the unaided eye. The compound melts at 238°-240° (corr.).

0.2351 gram substance gave 17.10 cc. nitrogen at 26° and 761 mm.

	Calculated for $C_{11}H_{10}Br_2N_2O$.	Found.
Nitrogen	8.09	8.07

6,8-Dibrom-2-isopropyl-4-ketodihydroquinazoline,



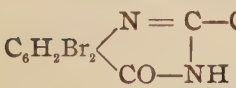
.—The tube was prepared in the same way as for the *n*-propyl compound, heated to 200° for ten and a half hours and to 210° for five and a half hours. The appearance of the tube indicated only a partial condensation, and it was returned to the furnace and heated for two hours to 220°. This temperature caused a partial decomposition and the yield was only moderately good.

The compound separates in a felt of microscopic, perfectly white hairs. These crystals must be quite highly magnified to show their structure clearly. They melt with decomposition at 259°-260° (corr.).

0.2228 gram substance gave 15.90 cc. nitrogen at 26° and 761 mm.

	Calculated for $C_{11}H_{10}Br_2N_2O$.	Found.
Nitrogen	8.09	7.92

6,8-Dibrom-2-isobutyl-4-ketodihydroquinazoline,



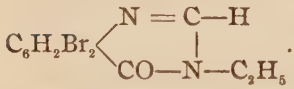
.—Three grams of the nitrile and 3 cc. of isovaleric anhydride were heated to 200° for ten and a half hours and to 210° for five and a half hours. The condensation did not seem to be complete and the tube was returned to the oven and heated to 215°-220° for about two hours. The dark-colored, crystalline condensation product was purified as usual. The yield was only moderately good. This quinazoline separates in white, microscopic needles, which melt at 230°-231.5°.

0.1999 gram substance gave 14.10 cc. nitrogen at 26° and 761 mm.

	Calculated for $C_{12}H_{12}Br_2N_2O$.	Found.
Nitrogen	7.77	7.82

Ethers of the 6,8-Dibrom-2-alkyl-4-ketodihydroquinazolines.—The ethers of these quinazolines were prepared by the action of ethyl iodide on their sodium salts. The reactions were carried out in alcoholic solution and in sealed tubes.

Ethyl Ether of 6,8-Dibrom-4-ketodihydroquinazoline,

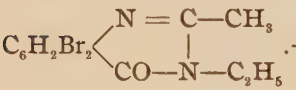


.—About 0.5 gram of the quinazoline was placed in the tube and an alcoholic solution of sodium hydroxide added until the compound just dissolved on gentle warming, and an excess of ethyl iodide added. The tube was heated to 100°-104° for two and a half hours, and, on cooling, the beautifully crystalline ether separated in the tube. The small, clear needles were washed well with water and with 95 per cent. alcohol, when they were snow-white and seemed to require no further purification. They melted sharply at 229°-230° (corr.).

0.1836 gram substance gave 14.60 cc. nitrogen at 26° and 756 mm.

	Calculated for $C_{10}H_8Br_2N_2O$.	Found.
Nitrogen	8.43	8.70

Ethyl Ether of 6,8-Dibrom-2-methyl-4-ketodihydroquinazoline,



.—One-half gram of the methyl quinazoline was treated with alcoholic caustic soda solution and ethyl iodide, as described above, and the tube was heated to 100°-105° for two and a half hours. The ether, however, did not separate out on cooling the tube, and the alcoholic solution was evaporated to a small bulk, when well-formed, light brown needles separated. These were recrystallized from alcohol, but still remained slightly colored. The quantity at hand was not sufficient for further purification, though it is probable that bone-char would have cleared the needles. The compound begins to decompose at about 170° when heated slowly, but does not melt at 290°.

Ethyl Ether of 6,8-Dibrom-2-methyl-4-thioketodihydroquinazoline, $C_6H_2Br_2\langle \begin{matrix} N=C-CH_3 \\ | \\ CS-N-C_2H_5 \end{matrix}$.—This ether was prepared in a similar manner to those already described. The compound separated in the tube in light yellow needles, which begin to decompose at about 305°, but do not melt completely when heated to 360°.

SUMMARY OF RESULTS.

The work outlined in the preceding pages has shown:

I. That under certain conditions of temperature and pressure anthranilicnitrile and fatty acid anhydrides react to form the 2-alkyl-4-ketodihydroquinazolines.

II. That acylanthranilicnitriles pass over into the corresponding ketodihydroquinazolines when warmed with alkaline hydrogen peroxide solution, the probable intermediate product being the acylanthranilamide.

III. That the 2-alkyl-4-thioketodihydroquinazolines (new series) may be produced:

(*a*) By the action of thio fatty acids upon anthranilicnitriles.

(*b*) By the action of fatty acid anhydrides upon orthoaminobenzthiamide.

(*c*) By the action of hydrogen sulphide upon the acylanthranilicnitriles.

(*d*) By heating together, under pressure, fatty acid anhydrides, sodium sulphide, and anthranilicnitrile.

IV. That 3,5-dibromanthranilic acid may be prepared by the direct action upon anthranilic acid of the calculated quantity of nascent bromine, no isomeric brominated acids or tribromaniline being simultaneously produced.

V. That 3,5-dibromanthranilicnitrile may be obtained in good yield from anthranilicnitrile by the action of nascent bromine.

VI. That 6,8-dibrom-2-algyl-4-ketodihydroquinazolines are produced by the action of fatty acid anhydrides upon 3,5-dibromanthranilicnitrile at elevated temperatures in sealed tubes.

VII. That the thio fatty acids and 3,5-dibromanthranilicnitrile yield the brominated 2-alkyl-4-thioketodihydroquinazolines.

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BIOGRAPHICAL

The author of this dissertation was born in Shubuta, Mississippi, December first, 1873, and entered the Mississippi Agricultural and Mechanical College in September 1889, receiving the degree of Bachelor of Science in 1893 and of Master of Science in 1895.

He was appointed third assistant chemist in the State and College Chemical Laboratory in 1893, and was elected Professor of Chemistry and State Chemist in June 1899. The summer of 1896 was spent at the University of Virginia.

During the academic session of 1901-1902 and the summer session of 1902, he pursued graduate work in chemistry under the Faculty of Pure Science of Columbia University, and continued this work in absentia in 1902-1903.

He has participated in the publication of the following papers:

"The Synthesis of Alkylketodihydroquinazolines from Anthranilicnitrile" (with Marston T. Bogert), *J. Am. Chem. Soc.*, **24**, 1031.

"The Synthesis of Alkylthioketodihydroquinazolines from Anthranilicnitrile" (with Marston T. Bogert and H. C. Breneman), *J. Am. Chem. Soc.*, **25**, 372.

"The 3,5-Bibrom-2-aminobenzoic Acid, Its Nitrile, and the Synthesis of Quinazolines from the Latter" (with Marston T. Bogert), *J. Am. Chem. Soc.* **25**, 935.